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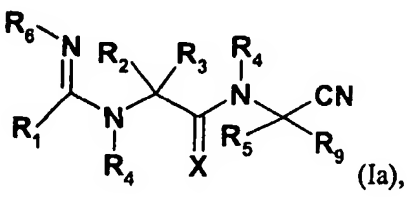
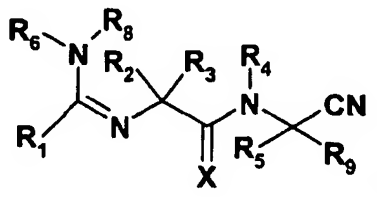
(54) Title: COMPOUNDS USEFUL AS REVERSIBLE INHIBITORS OF CYSTEINE PROTEASES


(Ia),


(Ib)

(57) Abstract: Disclosed are novel cathepsin S, K, F, L and B reversible inhibitory compounds of the formulas (Ia) and (Ib) where R_1, R_2, R_3, R_4, R_5, R_6, R_8, R_9 and X aredefined herein. The compoundsare useful for treating autoimmune and other diseases. Also disclosed are processes for making such novel compounds.

WO 03/029200 A2

Compounds Useful As Reversible Inhibitors of Cysteine Proteases

APPLICATION DATA

This application claims benefit to US provisional application serial no. 60/326,538 filed 10/2/2001.

TECHNICAL FIELD OF THE INVENTION

This invention relates to amidino and guanidino peptidyl compounds active as cysteine protease inhibitors. The compounds are reversible inhibitors of the cysteine protease cathepsin S, K, F, L and B are therefore useful in the treatment of autoimmune and other diseases. The invention also relates to processes for preparing such compounds and pharmaceutical compositions comprising them.

BACKGROUND OF THE INVENTION

Cathepsin S and cathepsin K are members of the papain family, within the papain superfamily of cysteine proteases. The papain family is the largest group of cysteine proteases and includes proteases such as cathepsins B, H, K, L, O and S. (A.J. Barrett et al., 1996, Perspectives in Drug Discovery and Design, 6, 1). The cysteine proteases have important roles in human biology and diseases including atherosclerosis, emphysema, osteoporosis, chronic inflammation and immune disorders (H.A. Chapman et al., 1997, Ann. Rev. Physiol., 59, 63). Cathepsin S plays a key role in regulating antigen presentation and immunity (H.A. Chapman, 1998, Current Opinion in Immunology, 10, 93; R. J. Riese et al., 1998, J. Clin. Invest., 101, 2351; R.J. Riese et al., 1996, Immunity, 4, 357). Cathepsin S deficient mice have impaired invariant chain degradation resulting in decreased antigen presentation and germinal center formation, and diminished susceptibility to collagen-induced arthritis indicating the therapeutic potential for a cathepsin S inhibitor (G. Shi et al., 1999, Immunity, 10, 197; T.Y. Nakagawa et al, 1999, Immunity, 10, 207)

The specificity of the immune response relies on processing of foreign protein and presentation of antigenic peptide at the cell surface. Antigenic peptide is presented bound to MHC Class II, a heterodimeric glycoprotein expressed in certain antigen presenting cells of hematopoietic lineage, such as B cells, macrophages and dendritic cells. Presentation of antigen to effector cells, such as T-cells, is a fundamental step in recognition of non-self and thus initiation of the immune response.

Recently MHC Class II heterodimers were shown to associate intracellularly with a third molecule designated invariant chain. Invariant chain facilitates Class II transport to the endosomal compartment and stabilizes the Class II protein prior to loading with antigen. Invariant chain interacts directly with Class II dimers in the antigen-binding groove and therefore must be proteolyzed and removed or antigen cannot be loaded or presented. Current research suggests that invariant chain is selectively proteolyzed by cathepsin S, which is compartmentalized with MHC Class II complexes within the cell. Cathepsin S degrades invariant chain to a small peptide, termed CLIP, which occupies the antigen – binding groove. CLIP is released from MHC Class II by the interaction of MHC Class II with HLA-DM, a MHC-like molecule thus freeing MHC Class II to associate with antigenic peptides. MHC Class II-antigen complexes are then transported to the cell surface for presentation to T-cells, and initiation of the immune response.

Cathepsin S, through proteolytic degradation of invariant chain to CLIP, provides a fundamental step in generation of an immune response. It follows that inhibition of antigen presentation via prevention of invariant chain degradation by cathepsin S could provide a mechanism for immuno-regulation. Control of antigen-specific immune responses has long been desirable as a useful and safe therapy for autoimmune diseases. Such diseases include Crohn's disease and arthritis, as well as other T-cell-mediated immune responses (C. Janeway and P. Travers, 1996, Immunobiology, The Immune System in Health and Disease, Chapter 12). Furthermore, cathepsin S, which has broad pH specificity, has been implicated in a variety of other diseases involving extracellular proteolysis, such as Alzheimer's disease (U. Muller-Ladner et al., 1996, Perspectives in

Drug Discovery and Design, 6, 87), atherosclerosis (G.K. Sukhova et al., 1998, J. Clin. Invest., 102, 576) and endometriosis (WO 9963115, 1999).

A cathepsin S inhibitor has been found to block the rise in IgE titers and eosinophil infiltration in the lung in a mouse model of pulmonary hypersensitivity, suggesting that cathepsin S may be involved in asthma (R.J. Riese et al., J. Clin. Investigation,1998, 101, 2351).

Another cysteine protease, cathepsin F has been found in macrophages and is also involved in antigen processing. It has been postulated that cathepsin F in stimulated lung macrophages and possibly other antigen presenting cells could play a role in airway inflammation (G.-P. Shi et al., J. Exp. Med., 2000, 191, 1177).

Cathepsin K, another cysteine protease has been found to be highly expressed in osteoclasts and to degrade bone collagen and other bone matrix proteins. Inhibitors of cathepsin K have been shown to inhibit bone resorption in mice. Therefore, cathepsin K may play a role in osteoclastic bone resorption and cathepsin K inhibitors may be useful in the treatment of diseases involving bone resorption such as osteoporosis (F. Lazner et al., Human Molecular Genetics, 1999, 8, 1839).

Cysteine proteases are characterized by having a cysteine residue at the active site which serves as a nucleophile. The active site also contains a histidine residue. The imidazole ring on the histidine serves as a base to generate a thiolate anion on the active site cysteine, increasing its nucleophilicity. When a substrate is recognized by the protease, the amide bond to be cleaved is directed to the active site, where the thiolate attacks the carbonyl carbon forming an acyl-enzyme intermediate and cleaving the amide bond, liberating an amine. Subsequently, water cleaves the acyl-enzyme species regenerating the enzyme and liberating the other cleavage product of the substrate, a carboxylic acid.

Inhibitors of cysteine proteases contain a functionality that can react reversibly or irreversibly with the active site cysteine. Examples of reactive functionalities that have

been described (D. Rasnick, 1996, Perspectives in Drug Discovery and Design, 6, 47) on cysteine protease inhibitors include peptidyl diazomethanes, epoxides, monofluoroalkanes and acyloxymethanes, which irreversibly alkylate the cysteine thiol. Other irreversible inhibitors include Michael acceptors such as peptidyl vinyl esters and other carboxylic acid derivatives (S. Liu et al., J. Med Chem., 1992, 35, 1067) and vinyl sulfones (J.T. Palmer et al., 1995, J. Med Chem., 38, 3193).

Reactive functionalities that form reversible complexes with the active site cysteine include peptidyl aldehydes (R.P. Hanzlik et al., 1991, Biochim. Biophys. Acta., 1073, 33), which are non-selective, inhibiting both cysteine and serine proteases as well as other nucleophiles. Peptidyl nitriles (R.P. Hanzlik et al., 1990, Biochim. Biophys. Acta., 1035, 62) are less reactive than aldehydes and therefore more selective for the more nucleophilic cysteine proteases. Various reactive ketones have also been reported to be reversible inhibitors of cysteine proteases (D. Rasnick, 1996, ibid). In addition to reacting with the nucleophilic cysteine of the active site, reactive ketones may react with water, forming a hemiketal which may act as a transition state inhibitor.

Examples of cathepsin S inhibitors have been reported. J.L. Klaus et al. (WO 9640737) described reversible inhibitors of cysteine proteases including cathepsin S, containing an ethylene diamine. In US Patent No. 5,776,718 to Palmer et al. there is disclosed in it's broadest generic aspect a protease inhibitor comprising a targeting group linked through a two carbon atom chain to an electron withdrawing group (EWG). The compounds of the present application are structurally distinct and thus excluded from the 5,776,718 patent with particular embodiments possessing unexpectedly greater activity than the closest compounds of the prior art. Other examples of cathepsin S inhibitors have been reported by E.T. Altmann et al, (WO 9924460, 1999) which describes dipeptide nitriles asserted to have activity as inhibitors of Cathepsins B, K, L and S. Axys publications WO 00/55125 and 00/55126 disclose peptidyl nitriles for cathepsin inhibition which possess spirocarbocyclic and spiroheterocyclic moieties at P1, Axys publications WO 01/19808 and WO 01/19796 disclose peptidyl nitriles possessing mandatory sulfonyl groups at P2.

Additional peptidyl nitriles have been reported as protease inhibitors. For example, both nitriles and ketoheterocycles are described by B.A. Rowe et al. (US 5,714,471) as protease inhibitors useful in the treatment of neurodegenerative diseases. Peptidyl nitriles are reported by B. Malcolm et al. (WO 9222570) as inhibitors of picornavirus protease. B.J. Gour-Salin (Can. J. Chem., 1991, 69, 1288) and T.C. Liang (Arch. Biochim. Biophys., 1987, 252, 626) described peptidyl nitriles as inhibitors of papain

None of the aforementioned publications disclose compounds possessing a mandatory guanidino or amidino structure at the P3 position.

A reversible inhibitor presents a more attractive therapy than irreversible inhibitors. Even compounds with high specificity for a particular protease can bind non-target enzymes. An irreversible compound could therefore permanently inactivate a non-target enzyme, increasing the likelihood of toxicity. Furthermore, any toxic effects resulting from inactivation of the target enzyme would be mitigated by reversible inhibitors, and could be easily remedied by modified or lower dosing. Finally, covalent modification of an enzyme by an irreversible inhibitor could potentially generate an antibody response by acting as a hapten.

In light of the above, there is a clear need for compounds which reversibly and selectively inhibit cysteine proteases such as cathepsin S and cathepsin K for indications in which these proteases exacerbate disease.

BRIEF DESCRIPTION OF THE INVENTION

It is therefore an object of this invention to provide novel compounds according to the formula (Ia/Ib) as described herein which reversibly inhibit the cysteine proteases cathepsin S, K, F, L and B. It is a further object of the invention to provide methods for treating diseases and pathological conditions exacerbated by these cysteine proteases

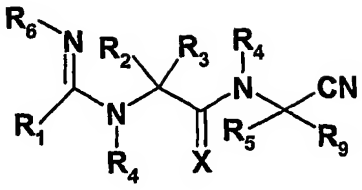
such as, but not limited, to rheumatoid arthritis, multiple sclerosis, asthma and osteoporosis. It is yet a further object of the invention to provide novel processes for preparation of the above-mentioned novel compounds.

DETAILED DESCRIPTION OF THE INVENTION

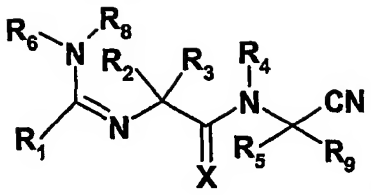
A proposed mechanism of action of the cysteine protease inhibitors of this invention is that the inhibitors contain a functionality that can react (reversibly or irreversibly) with the active site cysteine. The reactive functionality is attached to a peptide or peptide mimic that can be recognized and accommodated by the region of the protease surrounding the active site. The nature of both the reactive functionality and the remaining portion of the inhibitor determine the degree of selectivity and potency toward a particular protease.

Given the similarity of the active sites in cysteine proteases, it may be anticipated that a given class of inhibitors might have activity against more that one cysteine protease. It may also be expected that due to structural differences between individual cysteine proteases, different compounds of the invention may have different inhibitory potencies against different cysteine proteases. Thus some of the compounds of the invention may also be expected to be most effective in treating diseases mediated by cysteine proteases that they inhibit most potently. The activity of particular compounds disclosed herein against cysteine proteases such as cathepsin S, K, F, L and B may be determined by the screens described in the section entitled "Assessment of Biological Properties."

Accordingly, in a first generic aspect of the invention, there are provided compounds of formula (Ia) or (Ib):



(Ia),



(Ib)

wherein:

R_1 is a bond, hydrogen, C1-10 alkyl, C1-10 alkoxy, aryloxy, C3-8 cycloalkyl, C3-8 cycloalkyloxy, aryl, benzyl, tetrahydronaphthyl, indenyl, indanyl, C1-10alkylsulfonylC1-10alkyl, C3-8cycloalkylsulfonylC1-10alkyl, arylsulfonylC1-10alkyl, heterocyclyl selected from azepanyl, azocanyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, indolinyl, pyranyl, tetrahydropyranyl, tetrahydrothiopyranyl, thiopyranyl, furanyl, tetrahydrofuranyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, tetrazolyl, pyrazolyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, benzoxazolyl, benzisoxazolyl, quinolinyl, tetrahydroquinolinyl, isoquinolinyl, tetrahydroisoquinolinyl, quinazolinyl, tetrahydroquinazolinyl and quinoxalinyl, heterocyclyloxy wherein the heterocyclyl moiety is selected from those herein described in this paragraph, hydroxy or amino; wherein R_1 is optionally substituted by one or more R_a;

R_a is a bond, C1-10 alkyl, C3-8 cycloalkyl, aryl, tetrahydronaphthyl, indenyl, indanyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, indolinyl, furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, benzoxazolyl, benzisoxazolyl, quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, C1-10 alkoxy, C1-10alkanoyl, C1-10alkanoyloxy, aryloxy, benzyloxy, C1-10 alkoxycarbonyl, aryloxycarbonyl, aroyloxy, carbamoyl wherein the nitrogen atom may be independently mono or

di-substituted by C1-10 alkyl, aryl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, indolinyl, furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl, isoquinolinyl, quinazolinyl or quinoxalinyl,

or R_a is C1-10 alkanoylamino, aroylamino, C1-10 alkylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, arylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, ureido wherein either nitrogen atom may be independently substituted by C1-10 alkyl, aryl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, indolinyl, furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl, isoquinolinyl, quinazolinyl or quinoxalinyl,

or R_a is C1-10 alkoxycarbonylamino, aryloxycarbonylamino, C1-10 alkylcarbamoyloxy, arylcarbamoyloxy, C1-10 alkylsulfonylamino, arylsulfonylamino, C1-10 alkylaminosulfonyl, arylaminosulfonyl, amino wherein the nitrogen atom may be independently mono or di-substituted by C1-10 alkyl, aryl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, indolinyl, furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl, isoquinolinyl, quinazolinyl or quinoxalinyl,

or R_a is halogen, hydroxy, oxo, carboxy, cyano, nitro, carboxamide, amidino or guanidino, R_a may be further optionally substituted by one or more R_b;

with the proviso that R_1 and R_a simultaneously cannot be a bond;

R_b is a C1-6 saturated or unsaturated branched or unbranched carbon chain optionally partially or fully halogenated wherein one or more carbon atoms are optionally replaced by O, N, S(O), $S(O)_2$ or S and wherein said chain is optionally independently substituted with 1-2 oxo groups, $-NH_2$, or one or more C1-4 alkyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, indolinyl, furanyl, thienyl, pyrrolyl,

oxazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl, isoquinolinyl, quinazolinyl or quinoxalinyl;

or R_b is C3-6 cycloalkyl, aryl, aryloxy, benzyloxy, halogen, hydroxy, oxo, carboxy, cyano, nitro, mono-C1-5alkylamino, di-C1-5alkylamino, carboxamide, amidino or guanidino;

R_2 is hydrogen or C1-3 alkyl;

R_3 is a bond, hydrogen, alkyl wherein one or more carbon atoms are optionally replaced by O, S or N wherein it shall be understood if N is not substituted by R_c then it is NH, or R_3 is C2-10alkylene, heterocyclylC1-5 alkyl wherein the heterocyclic moiety is selected from pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, 8-aza-bicyclo[3.2.1]octane, silinane, piperazinyl, indolinyl, furanyl, tetrahydrofuranyl, pyranyl, tetrahydropyranyl, tetrahydrothiopyranyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, dihydrobenzofuranyl, octohydrobenzofuranyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, tetrahydroquinolinyl, quinolinyl, tetrahydroisoquinolinyl, isoquinolinyl, quinazolinyl and quinoxalinyl, C3-8 cycloalkyl, arylC1-5alkyl or aryl wherein R_3 is optionally substituted by one or more R_c;

R_c is C3-8 cycloalkyl, aryl, indanyl, indenyl, bicyclo[2.2.1]heptanyl, bicyclo[2.2.2]octanyl, bicyclo[4.1.0]heptanyl, bicyclo[3.1.0]hexanyl, bicyclo[1.1.1]pentanyl, spiroC8-12 cycloalkyl, cubanyl, 1,2,3,4-tetrahydronaphthyl, decahydronaphthyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, indolinyl, furanyl, tetrahydrofuranyl, pyranyl, tetrahydropyranyl, tetrahydrothiopyranyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, dihydrobenzofuranyl, octohydrobenzofuranyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, tetrahydroquinolinyl, quinolinyl,

tetrahydroisoquinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, aryloxy, aroyl, aryloxycarbonyl, aroyloxy,
or R_c is aroylamino, alkylthio, arylthio, aryloxycarbonylamino, arylcarbamoyloxy, arylsulfonylamino, arylaminosulfonyl, amino wherein the nitrogen atom may be independently mono or di-substituted by C1-10 alkyl, aryl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, indolinyl, furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl, isoquinolinyl, quinazolinyl or quinoxalinyl,
or R_c is halogen, hydroxy, oxo, carboxy, cyano, nitro, amidino or guanidino, R_c may be further optionally substituted by one or more R_d;

R_d is C1-5 alkyl, C3-6 cycloalkyl, aryl, arylC1-5alkyl, C1-5 alkoxy, aryloxy, arylC1-5alkoxy, aroyl, amino, halogen, hydroxy, oxo, carboxy, cyano, nitro, amidino or guanidino;

R_2 and R_3 together with the carbon they are attached optionally form a nonaromatic 5-7 membered cycloalkyl or heterocyclic ring;

each R_4 is independently hydrogen, hydroxy or C1-3 alkyl;

R_5 is hydrogen, alkyl, alkoxy, alkoxyalkyl or arylalkyl;

R_9 is hydrogen, alkyl wherein one or more carbon atoms are optionally replaced by O, S or N wherein it shall be understood if N is not substituted by R_e then it is NH, or R_9 is cycloalkyl, aryl, heterocyclyl, aryl, heteroaryl or cyano, wherein R_9 is optionally substituted by one or more R_e;

R_e is selected from alkyl, cycloalkyl, aryl, aroyl, heterocyclyl, heteroaryl, halogen, hydroxy, oxo, carboxy, cyano, nitro, amidino and guanidino, R_e may be further optionally substituted by one or more R_f;

R_f is selected from alkyl, cycloalkyl, aryl optionally substituted by one or more groups selected from halogen, methyl or methoxy, heterocyclyl, heteroaryl, alkoxy, aryloxy, aroyl, arylalkoxy, alkoxycarbonyl, aryloxycarbonyl, alkanoyloxy, aroyloxy, carbamoyl wherein the nitrogen atom may be independently mono or di-substituted by alkyl, aryl, heterocyclyl or heteroaryl, alkanoylamino, aroylamino, alkylcarbamoyl, arylcarbamoyl, alkylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, arylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, ureido wherein either nitrogen atom may be independently substituted by alkyl, aryl, heterocyclyl or heteroaryl, alkoxycarbonylamino, aryloxycarbonylamino, alkylcarbamoyloxy, arylcarbamoyloxy, alkylsulfonylamino, arylsulfonylamino, alkylaminosulfonyl, arylaminosulfonyl, amino wherein the nitrogen atom may be independently mono or di-substituted by alkyl, aryl, heterocyclyl or heteroaryl, halogen, hydroxy, oxo, carboxy, cyano, nitro, amidino and guanidino;

or R_5 and R_9 together with the carbon they are attached form a 3 to 7-membered monocyclic carbocycle or a 7 to 14-membered bicyclic carbocycle optionally bridged, wherein either carbocycle is optionally benzofused and optionally substituted with one or more R_g;

R_g is selected from alkyl, aryl, alkoxycarbonyl, aryloxycarbonyl, arylalkoxycarbonyl, carbamoyl wherein the nitrogen atom may be optionally mono or di-substituted with a group selected from alkyl, cycloalkyl, aryl, arylalkyl, heterocyclyl, heteroaryl, halogen, hydroxy, carboxy and cyano;

R_6 is

hydrogen, hydroxy, nitrile or

a C1-6 saturated or unsaturated branched or unbranched alkyl optionally partially or fully halogenated wherein one or more C atoms are optionally replaced by O, NH, S(O), $S(O)_2$ or S and wherein said chain is optionally independently substituted with 1-2 oxo groups, -NH_2, one or more C1-4 alkyl, C3-7 cycloalkyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, indolinyl, pyranyl, thiopyranyl, furanyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl, isoquinolinyl, quinazolinyl, benzoxazolyl or quinoxalinyl;

wherein R_1 and R_6 in the formulas (Ia) or (Ib) optionally form a 4 to 8 membered mono- or 7-14 membered polycyclo heteroring system, each aromatic or nonaromatic, wherein each ring is optionally substituted by one or more R_7;

each R_7 and R_8 are independently:

hydrogen, C1-5 alkyl chain optionally interrupted by one or two N, O or $S(O)_m$ and optionally substituted by 1-2 oxo, amino, hydroxy, halogen, C1-4alkyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, indolinyl, pyranyl, thiopyranyl, furanyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl, isoquinolinyl, quinazolinyl, benzoxazolyl or quinoxalinyl,

aryl, aryloxy, aroyl, furanyl, thienyl, pyrrolyl, imidazolyl, pyridinyl, pyrimidinyl, C1-5 alkanoyl, C1-5 alkoxycarbonyl, aryloxycarbonyl, benzyloxycarbonyl, C1-5 alkanoylamino, aroylamino, C1-5 alkylthio, arylthio C1-5 alkylsulfonylamino, arylsulfonylamino, C1-5 alkylaminosulfonyl, arylaminosulfonyl, C3-6 cycloalkyl and benzyloxy
each of the aforementioned are optionally halogenated,
halogen, hydroxy, oxo, carboxy, nitrile, nitro or $NH_2C(O)$-;

m is 0, 1 or 2;

X is =O, =S or =N-R_6 wherein R_6 is as defined above, and

pharmaceutically acceptable derivatives thereof.

In another embodiment of the invention, there are provided novel compounds of the formula (Ia) or formula (Ib) as described immediately above, and wherein:

R_1 and R_6 of the formula (Ia) or formula (Ib) form:

a monocyclic 5, 6 or 7 membered aromatic or nonaromatic heterocyclic ring optionally substituted by R_7;

a bicyclic ring having one 5, 6 or 7 membered aromatic or nonaromatic heterocyclic ring fused to a second 5-7 membered aromatic or nonaromatic heterocyclic or carbocyclic ring wherein each ring is optionally independently substituted by one or more R_7;

or a tricyclic ring wherein the abovementioned bicyclic ring is further fused to a third 5-7 membered aromatic or nonaromatic heterocyclic or carbocyclic ring wherein each ring is optionally independently substituted by one or more R_7;

R_2 is hydrogen or methyl or ethyl;

R_3 is a bond, hydrogen, C1-10 alkyl wherein one or more carbon atoms are optionally replaced by O, S or N, or R_3 is C2-5alkylene, C3-7 cycloalkyl, heterocyclylC1-5 alkyl wherein the heterocyclic moiety is selected from pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, 8-aza-bicyclo[3.2.1]octane, silinane, piperazinyl, indolinyl, furanyl, tetrahydrofuranyl, pyranyl, tetrahydropyranyl, tetrahydrothiopyranyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, pyridinyl, pyrimidinyl, pyrazinyl and indolyl, arylC1-3alkyl or aryl wherein R_3 is optionally substituted by one or more R_6;

R_c is C3-7 cycloalkyl, aryl, indanyl, indenyl, bicyclo[2.2.1]heptanyl, bicyclo[2.2.2]octanyl, bicyclo[4.1.0]heptanyl, bicyclo[3.1.0]hexanyl, bicyclo[1.1.1]pentanyl, spiroC8-10 cycloalkyl, cubanyl, 1,2,3,4-tetrahydronaphthyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, indolinyl, furanyl, tetrahydrofuranyl, pyranyl, tetrahydropyranyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, aryloxy, aroyl, aryloxycarbonyl, aroyloxy,
or R_c is aroylamino, arylthio, aryloxycarbonylamino, arylcarbamoyloxy, arylsulfonylamino, arylaminosulfonyl, amino wherein the nitrogen atom may be independently mono or di-substituted by C1-5 alkyl, aryl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, indolinyl, furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl, isoquinolinyl, quinazolinyl or quinoxalinyl,
or R_c is halogen, hydroxy, oxo, carboxy, cyano, nitro, amidino or guanidino, R_c may be further optionally substituted by one or more R_d;

R_d is C1-5 alkyl, C3-6 cycloalkyl, aryl, arylC1-4 alkyl, C1-5 alkoxy, aryloxy, arylC1-5alkoxy, aroyl, halogen, hydroxy, oxo or cyano;

R_4 is hydrogen or methyl;

R_9 is hydrogen, C1-12 alkyl wherein one or more carbon atoms are optionally replaced by O, S or N, C3-7 cycloalkyl, heterocyclyl selected from pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl and indolinyl, heteroaryl selected from furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, tetrazolyl, thiadiazolyl, pyridinyl, pyridazinyl,

pyrimidinyl, pyrazinyl, indolyl, isoindolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, purinyl, quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, carbazolyl, phenothiazinyl and phenoxazinyl, aryl or cyano, wherein R_9 is optionally substituted by one or more R_e;

R_e is selected from C1-8 alkyl, C3-7 cycloalkyl, aryl, aroyl, heterocyclyl selected from pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl and indolinyl; heteroaryl selected from furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, tetrazolyl, thiadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, indolyl, isoindolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, purinyl, quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, carbazolyl, phenothiazinyl and phenoxazinyl, halogen, hydroxy, oxo, carboxy, cyano, nitro, amidino and guanidino, R_e may be further optionally substituted by one or more R_f;

R_f is selected from C1-8 alkyl, C3-7 cycloalkyl, aryl optionally substituted by one or more groups selected from halogen, methyl or methoxy, heterocyclyl selected from pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl and indolinyl; heteroaryl selected from furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, tetrazolyl, thiadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, indolyl, isoindolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, purinyl, quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, carbazolyl, phenothiazinyl and phenoxazinyl, C1-8 alkoxy, aryloxy, aroyl, arylC1-8alkoxy, C1-8 alkoxycarbonyl, aryloxycarbonyl, C1-8 alkanoyloxy, aroyloxy, carbamoyl wherein the nitrogen atom may be independently mono or di-substituted by C1-8 alkyl, aryl, heterocyclyl selected from pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl and indolinyl, or heteroaryl selected from furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl,

triazolyl, tetrazolyl, thiadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, indolyl, isoindolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, purinyl, quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, carbazolyl, phenothiazinyl and phenoxazinyl, C1-8 alkanoylamino, aroylamino, C1-8 alkylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, arylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, ureido wherein either nitrogen atom may be independently substituted by alkyl, aryl, heterocyclyl selected from pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl and indolinyl, or heteroaryl selected from furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, tetrazolyl, thiadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, indolyl, isoindolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, purinyl, quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, carbazolyl, phenothiazinyl and phenoxazinyl, alkoxycarbonylamino, aryloxycarbonylamino, alkylcarbamoyloxy, arylcarbamoyloxy, alkylsulfonylamino, arylsulfonylamino, alkylaminosulfonyl, arylaminosulfonyl, amino wherein the nitrogen atom may be independently mono or di-substituted by alkyl, aryl, heterocyclyl selected from pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl and indolinyl, or heteroaryl selected from furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, tetrazolyl, thiadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, indolyl, isoindolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, purinyl, quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, carbazolyl, phenothiazinyl and phenoxazinyl, halogen, hydroxy, oxo, carboxy, cyano, nitro, amidino and guanidino;

or R_5 and R_9 together with the carbon they are attached form a 3 to 7-membered monocyclic carbocycle or a 7 to 14-membered bicyclic carbocycle optionally bridged,

wherein either carbocycle is optionally benzofused and optionally substituted with one or more R_g;

R_g is selected from C1-8 alkyl, aryl, C1-8 alkoxycarbonyl, aryloxycarbonyl, arylC1-8alkoxycarbonyl, carbamoyl wherein the nitrogen atom may be optionally mono or di-substituted with a group selected from C1-8 alkyl, C3-7 cycloalkyl, aryl, arylC1-8alkyl, heterocyclyl selected from pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl and indolinyl, or heteroaryl selected from furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, tetrazolyl, thiadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, indolyl, isoindolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, purinyl, quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, carbazolyl, phenothiazinyl and phenoxazinyl, halogen, hydroxy, carboxy and cyano;

R_7 and R_8 are independently hydrogen, C1-5 alkyl, C3-6 cycloalkyl, aryl, C1-5 alkoxy, aryloxy, benzyloxy each of the aforementioned are optionally halogenated, halogen, hydroxy, oxo, carboxy, nitrile, nitro or $NH_2C(O)$-;

m is 0, 1 or 2 and

X is O or S.

In yet another embodiment of the invention, there are provided novel compounds of the formulas (Ia) or (Ib) as described immediately above, and wherein:

R_1 and R_6 of the formula (Ia) or Formula (Ib) form:

a monocyclic 5 or 6 membered aromatic or nonaromatic heterocyclic ring optionally substituted by R_7;

a bicyclic ring having one 5, 6 or 7 membered aromatic or nonaromatic heterocyclic ring fused to a second 5-6 membered aromatic or nonaromatic heterocyclic or carbocyclic ring wherein each ring is optionally independently substituted by one or more R_7;

or a tricyclic ring having one 5, 6 or 7 membered aromatic or nonaromatic heterocyclic ring fused to a 5-6-membered aromatic or nonaromatic carbocyclic ring which in turn is fused to a 5, 6 or 7 membered aromatic or nonaromatic heterocyclic ring;

R_2 is hydrogen or methyl;

R_3 is a bond, hydrogen, C1-10 alkyl wherein one or more carbon atoms are optionally replaced by O, S or N, or R_3 is C2-5alkylene, C4-6 cycloalkyl, heterocyclylC1-5 alkyl wherein the heterocyclic moiety is selected from pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, 8-aza-bicyclo[3.2.1]octane, silinane, piperazinyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydrothiopyranyl and indolyl, or arylC1-2alkyl wherein R_3 is optionally substituted by one or more R_c;

R_c is C5-6 cycloalkyl, phenyl, naphthyl, indanyl, bicyclo[2.2.1]heptanyl, bicyclo[2.2.2]octanyl, bicyclo[4.1.0]heptanyl, bicyclo[3.1.0]hexanyl, bicyclo[1.1.1]pentanyl, spiroC8-10 cycloalkyl, cubanyl, 1,2,3,4-tetrahydronaphthyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, indolinyl, furanyl, tetrahydrofuranyl, pyranyl, tetrahydropyranyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, phenoxy, naphthyloxy, benzoyl, phenoxycarbonyl, benzoyloxy, benzoylamino, phenylthio, aryloxycarbonylamino, arylcarbamoyloxy, arylsulfonylamino, arylaminosulfonyl, amino wherein the nitrogen atom may be independently mono or di-substituted by C1-5 alkyl or aryl,

or R_c is halogen, hydroxy, oxo, carboxy, cyano, nitro, amidino or guanidino, R_c may be further optionally substituted by one or more R_d;

R_d is C1-3 alkyl, C3-6 cycloalkyl, phenyl, benzyl, C1-3 alkoxy, phenoxy, phenylC1-3alkoxy, benzoyl, halogen, hydroxy, oxo or cyano;

R_4 is hydrogen;

R_5 is hydrogen, C1-8 alkyl, C1-3 alkoxyC1-3 alkyl, C1-8 alkoxy, phenylC1-5 alkyl or naphthylC1-5 alkyl;

R_9 is hydrogen, C1-12 alkyl wherein one or more carbon atoms are optionally replaced by O, S or N, C3-7 cycloalkyl, heterocyclyl selected from pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl and indolinyl; heteroaryl selected from furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl, isoquinolinyl, quinazolinyl and quinoxalinyl, aryl or cyano, wherein R_9 is optionally substituted by one or more R_e;

R_e is selected from C1-5 alkyl, C3-7 cycloalkyl, aryl, aroyl, heterocyclyl selected from pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl and indolinyl; heteroaryl selected from furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl, isoquinolinyl, quinazolinyl and quinoxalinyl, halogen, hydroxy, oxo, carboxy, cyano, nitro, amidino and guanidino, R_e may be further optionally substituted by one or more R_f;

R_f is selected from C1-5 alkyl, C3-7 cycloalkyl, aryl optionally substituted by one or more groups selected from halogen, methyl or methoxy, heterocyclyl selected from pyrrolidinyl, piperidinyl, morpholinyl,

thiomorpholinyl, piperazinyl and indolinyl, heteroaryl selected from furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl, isoquinolinyl, quinazolinyl and quinoxalinyl, C1-5 alkoxy, aryloxy, aroyl, arylC1-5alkoxy, C1-5 alkoxycarbonyl, aryloxycarbonyl, C1-5 alkanoyloxy, aroyloxy, carbamoyl wherein the nitrogen atom may be independently mono or di-substituted by C1-5 alkyl, aryl, heterocyclyl selected from pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl and indolinyl or heteroaryl selected from furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl, isoquinolinyl, quinazolinyl and quinoxalinyl, C1-5 alkanoylamino, aroylamino, C1-5 alkylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, arylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, ureido wherein either nitrogen atom may be independently substituted by C1-5 alkyl, aryl, heterocyclyl selected from pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl and indolinyl, or heteroaryl selected from furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl, isoquinolinyl, quinazolinyl and quinoxalinyl, C1-5 alkoxycarbonylamino, aryloxycarbonylamino, C1-5 alkylcarbamoyloxy, arylcarbamoyloxy, C1-5 alkylsulfonylamino, arylsulfonylamino, C1-5 alkylaminosulfonyl, arylaminosulfonyl, amino wherein the nitrogen atom may be independently mono or di-substituted by C1-5 alkyl, aryl, heterocyclyl selected from pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl and indolinyl, or heteroaryl selected from furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl,

isoquinolinyl, quinazolinyl and quinoxalinyl, halogen, hydroxy, oxo, carboxy, cyano, nitro, amidino and guanidino;

or R_5 and R_9 together with the carbon they are attached form a 3 to 7-membered monocyclic carbocycle or a 7 to 14-membered bicyclic carbocycle optionally bridged, wherein either carbocycle is optionally benzofused and optionally substituted with one or more R_g;

R_g is selected from C1-5 alkyl, aryl, C1-5 alkoxycarbonyl, aryloxycarbonyl, arylC1-5alkoxycarbonyl, carbamoyl wherein the nitrogen atom may be optionally mono or di-substituted with a group selected from C1-5 alkyl, C3-7 cycloalkyl, aryl, arylC1-5alkyl, heterocyclyl selected from pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl and indolinyl, or heteroaryl selected from furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl, isoquinolinyl, quinazolinyl and quinoxalinyl, halogen, hydroxy, carboxy and cyano;

R_7 and R_8 are independently hydrogen, C1-4 alkyl, C5-6 cycloalkyl, C1-4 alkoxy, halogen, hydroxy, oxo, carboxy, nitrile, nitro or $NH_2C(O)$-;
and
X is O.

In yet still another embodiment of the invention, there are provided novel compounds of the formulas (Ia) or (Ib) as described immediately above, and wherein:

R_1 and R_6 of the formula (Ia) or formula (Ib) form:

a bicyclic ring having one 5 or 6 membered aromatic or nonaromatic heterocyclic ring fused to a second 5-6 membered heteroaryl, heterocycle or phenyl ring;

or a tricyclic ring having one 5, 6 or 7 membered aromatic or nonaromatic heterocyclic ring fused to a 5-6-membered aromatic or nonaromatic carbocyclic ring which in turn is fused to a 5, 6 or 7 membered aromatic or nonaromatic heterocyclic ring;
wherein each ring is optionally independently substituted by one or two R_7

R_2 is hydrogen;

R_3 is a bond, C1-10 alkyl wherein one or more carbon atoms are optionally replaced by O, S or N, or R_3 is C2-4alkylene, C5-6 cycloalkyl, heterocyclylC1-3 alkyl wherein the heterocyclic moiety is selected from pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, 8-aza-bicyclo[3.2.1]octane, silinane, piperazinyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydrothiopyranyl and indolyl, benzyl or naphthylmethyl wherein R_3 is optionally substituted by one or more R_c;

R_c is C5-6 cycloalkyl, phenyl, naphthyl, indanyl, bicyclo[2.2.1]heptanyl, bicyclo[2.2.2]octanyl, bicyclo[4.1.0]heptanyl, bicyclo[3.1.0]hexanyl, bicyclo[1.1.1]pentanyl, spiroC8-10 cycloalkyl, cubanyl, 1,2,3,4-tetrahydronaphthyl, furanyl, tetrahydropyranyl, thienyl, oxazolyl, thiazolyl, imidazolyl, pyrimidinyl, indolyl, benzofuranyl, benzothienyl, benzthiazolyl, phenoxy, naphthyloxy, benzoyl, phenoxycarbonyl, benzoyloxy, benzoylamino, phenylthio, phenoxycarbonylamino, arylcarbamoyloxy, phenylsulfonylamino, phenylaminosulfonyl, amino wherein the nitrogen atom may be independently mono or di-substituted by C1-3 alkyl or phenyl,
or R_c is halogen, hydroxy, oxo, carboxy or cyano, R_c may be further optionally substituted by one or more R_d;

R_d is methyl, cyclopropyl, cyclohexyl, phenyl, benzyl, methoxy, phenoxy, benzyloxy, benzoyl, fluoro, chloro, oxo or cyano;

R_5 is hydrogen, C1-5 alkyl, C1-3 alkoxyC1-3 alkyl, benzyl or phenethyl;

R_9 is hydrogen, C1-12 alkyl wherein one or more carbon atoms are optionally replaced by O, S or N, C3-7 cycloalkyl, heterocyclyl selected from pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl and indolinyl; heteroaryl selected from furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl, isoquinolinyl, quinazolinyl and quinoxalinyl, phenyl, naphthyl or cyano, wherein R_9 is optionally substituted by one or more R_e;.

R_e is selected from C1-5 alkyl, C3-7 cycloalkyl, phenyl, naphthyl, aroyl, heterocyclyl selected from pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl and indolinyl; heteroaryl selected from furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl, isoquinolinyl, quinazolinyl and quinoxalinyl, C1-5 alkoxy, aryloxy, aroyl, arylC1-5alkoxy, heteroarylC1-5alkoxy, C1-5 alkoxycarbonyl, aryloxycarbonyl, C1-5 alkanoyloxy, aroyloxy, carbamoyl wherein the nitrogen atom may be independently mono or di-substituted by C1-5 alkyl, aryl, heterocyclyl selected from piperidinyl, morpholinyl and piperazinyl or heteroaryl selected from furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl and isoquinolinyl, C1-5 alkanoylamino, aroylamino, C1-5 alkylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, arylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, arylC1-5 alkylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, ureido wherein either nitrogen atom may be independently substituted by C1-5 alkyl, aryl, heterocyclyl selected from piperidinyl, morpholinyl and piperazinyl or heteroaryl selected from furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl and isoquinolinyl, halogen, hydroxy,

oxo, nitro, carboxy and cyano, R_e may be further optionally substituted by one or more R_f;

R_f is selected from C1-5 alkyl, C3-7 cycloalkyl, phenyl optionally substituted by one or more groups selected from halogen, methyl or methoxy, naphthyl optionally substituted by one or more groups selected from halogen, methyl or methoxy, heterocyclyl selected from pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl and indolinyl; heteroaryl selected from furanyi, thienyi, pyrrolyi, oxazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl, isoquinolinyl, quinazolinyl and quinoxalinyl, C1-5 alkoxy, aryloxy, arylC1-5alkoxy, C1-5 alkoxycarbonyl, aryloxycarbonyl, C1-5 alkanoyloxy, aroyloxy, carbamoyl wherein the nitrogen atom may be independently mono or di-substituted by C1-5 alkyl, aryl, heterocyclyl selected from piperidinyl, morpholinyl and piperazinyl or heteroaryl selected from furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl and isoquinolinyl, C1-5 alkanoylamino, aroylamino, C1-5 alkylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, arylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, ureido wherein either nitrogen atom may be independently substituted by C1-5 alkyl, aryl, heterocyclyl selected from piperidinyl, morpholinyl and piperazinyl or heteroaryl selected from furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl and isoquinolinyl, C1-5 alkoxycarbonylamino, aryloxycarbonylamino, C1-5 alkylcarbamoyloxy, arylcarbamoyloxy, C1-5 alkylsulfonylamino, arylsulfonylamino, C1-5 alkylaminosulfonyl, arylaminosulfonyl, amino wherein the nitrogen atom may be independently mono or di-substituted by C1-5 alkyl, aryl, heterocyclyl

selected from pyrrolidinyl, piperidinyl, morpholinyl and piperazinyl or heteroaryl selected from furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl and isoquinolinyl, halogen, hydroxy, oxo, carboxy and cyano;

or R_5 and R_9 together with the carbon they are attached form a 3 to 7-membered monocyclic carbocycle or a 7 to 14-membered bicyclic carbocycle optionally bridged, wherein either carbocycle is optionally benzofused and optionally substituted with one or more R_g;

R_g is selected from C1-5 alkyl, phenyl, naphthyl, C1-5 alkoxycarbonyl, aryloxycarbonyl, arylC1-3alkoxycarbonyl, carbamoyl wherein the nitrogen atom may be optionally mono or di-substituted with a group selected from C1-5 alkyl, C3-6 cycloalkyl, phenyl, naphthyl, arylC1-3alkyl, heterocyclyl selected from pyrrolidinyl, piperidinyl, morpholinyl and piperazinyl or heteroaryl selected from furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl and isoquinolinyl, halogen, hydroxy, carboxy and cyano.

In yet a further embodiment of the invention, there are provided novel compounds of the formulas (Ia) or (Ib) as described immediately above, and wherein:

R_1 and R_6 of the formula (Ia) or Formula (Ib) form:
a bicyclic ring having one 5-6 membered aromatic or nonaromatic heterocyclic ring fused to a phenyl or 5-6 membered aromatic or nonaromatic heterocyclic ring;

a tricyclic ring having one 5-6 membered aromatic or nonaromatic heterocyclic ring fused to a 6-membered aromatic or nonaromatic carbocyclic ring which in turn is fused to a 5-6 membered aromatic or nonaromatic heterocyclic ring;

wherein each ring is optionally independently substituted by one or two R_7.

R_3 is a bond, C1-10 alkyl wherein one or more carbon atoms are optionally replaced by O, S or N, or R_3 is C2-4alkylene, C5-6 cycloalkyl, heterocyclylC1-2 alkyl wherein the heterocyclic moiety is selected from pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, 8-aza-bicyclo[3.2.1]octane, silinane, piperazinyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydrothiopyranyl and indolyl, benzyl or naphthylmethyl wherein R_3 is optionally substituted by one or more R_c;

R_c is C5-6 cycloalkyl, indanyl, bicyclo[2.2.1]heptanyl, bicyclo[2.2.2]octanyl, bicyclo[4.1.0]heptanyl, bicyclo[3.1.0]hexanyl, bicyclo[1.1.1]pentanyl, spiroC8-10 cycloalkyl, cubanyl, 1,2,3,4-tetrahydronaphthyl, thienyl, oxazolyl, thiazolyl, indolyl, benzofuranyl, benzothienyl, benzthiazolyl, phenoxy, benzoyl, phenoxycarbonyl, benzoyloxy, benzoylamino, phenylthio, phenoxycarbonylamino, phenylcarbamoyloxy, phenylsulfonylamino, phenylaminosulfonyl, amino wherein the nitrogen atom may be independently mono or di-substituted by methyl, ethyl or phenyl,
or R_c is fluoro, chloro or oxo, R_c may be further optionally substituted by one or more R_d;

R_d is methyl, cyclopropyl, phenyl, methoxy, fluoro, chloro or oxo;

R_9 is hydrogen, C1-12 alkyl wherein one or more carbon atoms are optionally replaced by O, S or N, C3-6 cycloalkyl, phenyl or cyano, wherein R_9 is optionally substituted by one or more R_e;

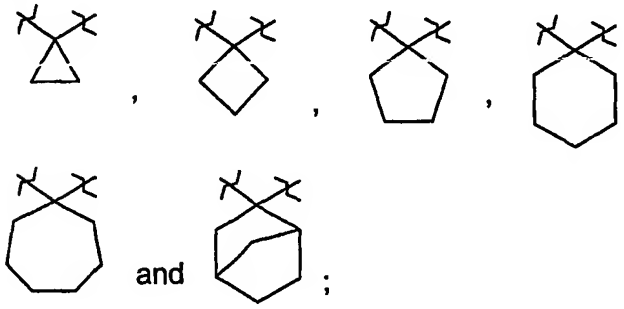
R_e is selected from C1-3 alkyl, C3-6 cycloalkyl, phenyl, naphthyl, aroyl, heterocyclyl selected from pyrrolidinyl, piperidinyl, morpholinyl, thio morpholinyl and piperazinyl; heteroaryl selected from furanyl, thienyl, pyrrolyl,

oxazolyl, thiazolyl, imidazolyl, pyridinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl and isoquinolinyl, C1-5 alkoxy, aryloxy, aroyl, arylC1-3alkoxy, heteroarylC1-3alkoxy, C1-5 alkoxycarbonyl, aryloxycarbonyl, C1-5 alkanoyloxy, aroyloxy, carbamoyl wherein the nitrogen atom may be independently mono or di-substituted by C1-5 alkyl, phenylor heteroaryl selected from furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl and indolyl, C1-5 alkanoylamino, aroylamino, C1-3 alkylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, arylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, arylC1-3alkylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, ureido wherein either nitrogen atom may be independently substituted by C1-5 alkyl or phenyl, C1-5 alkoxycarbonylamino, C1-5 alkylsulfonylamino, arylsulfonylamino, amino wherein the nitrogen atom may be independently mono or di-substituted by C1-5 alkyl, phenyl, naphthyl, heterocyclyl selected from piperidinyl, morpholinyl and piperazinyl or heteroaryl selected from furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, indolyl, halogen, hydroxy, oxo, nitro, carboxy and cyano, R_e may be further optionally substituted by one or more R_f;

R_f is selected from C1-3 alkyl, C5-6 cycloalkyl, phenyl optionally substituted by one or more groups selected from halogen or methyl, heterocyclyl selected from pyrrolidinyl, piperidinyl, morpholinyl and piperazinyl, heteroaryl selected from furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, pyrazinyl and indolyl, C1-5 alkoxy, aryloxy, arylC1-3alkoxy, C1-5 alkoxycarbonyl, aryloxycarbonyl, C1-5 alkanoyloxy, aroyloxy, carbamoyl wherein the nitrogen atom may be independently mono or di-substituted by C1-5 alkyl or aryl, C1-5 alkanoylamino, aroylamino, C1-5 alkylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, arylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, ureido wherein either nitrogen atom may be independently substituted by C1-5 alkyl or aryl, C1-5 alkoxycarbonylamino, aryloxycarbonylamino, C1-5 alkylcarbamoyloxy,

arylcarbamoyloxy, C1-5 alkylsulfonylamino, arylsulfonylamino, C1-5 alkylaminosulfonyl, arylaminosulfonyl, amino wherein the nitrogen atom may be independently mono or di-substituted by C1-5 alkyl or aryl, halogen, hydroxy, oxo, carboxy and cyano;

or R_5 and R_9 together with the carbon they are attached form a carbocyclic ring selected from :



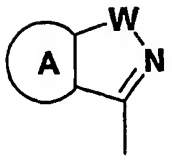
each carbocyclic ring being optionally benzofused and optionally substituted with one or more R_g;

R_g is selected from C1-5 alkyl, phenyl, C1-5 alkoxycarbonyl, aryloxycarbonyl, arylC1-3alkoxycarbonyl, carbamoyl wherein the nitrogen atom may be optionally mono or di-substituted with C1-5 alkyl, C3-6 cycloalkyl, phenyl, naphthyl or arylC1-3alkyl; halogen, hydroxy, carboxy and cyano.

In yet still a further embodiment of the invention, there are provided novel compounds of the formula (Ia) as described immediately above, and wherein:

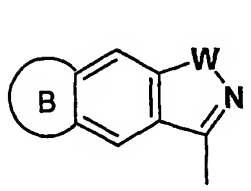
R_1 and R_6 of the formula (Ia) form:

the bicyclic ring:

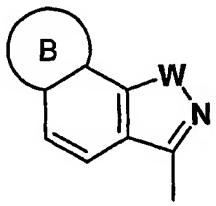


; wherein W is $-S(O)_n-$, >C(O), -O-C(O)-, -S-C(O)- or -NH-C(O)-, n is 0, 1 or 2, fused ring A is selected from phenyl, morpholinyl, pyridinyl, pyrimidinyl, pyrazinyl, piperidinyl, pyrazolyl, pyrrolyl, pyrrolidinyl, imidazolyl, oxazolyl, thienyl, furanyl and thiazinyl and wherein each ring is optionally independently substituted by one or two R_7.

or the tricyclic ring:



or



wherein W is $-S(O)_n-$, >C(O), -O-C(O)-, -S-C(O)- or -NH-C(O)-, n is 0, 1 or 2, fused ring B is selected from phenyl, morpholinyl, pyridinyl, pyrimidinyl, pyrazinyl, piperidinyl, pyrazolyl, pyrrolyl, pyrrolidinyl, imidazolyl, oxazolyl, thienyl, furanyl and thiazinyl and wherein each ring is optionally independently substituted by one or two R_7.

R_3 is a bond, methyl, ethyl, n-propyl, propenyl, butenyl, i-butenyl, C1-5 alkoxyC1-5 alkyl, C1-5 alkoxycarbonylC1-5 alkyl, C1-5 alkylthioC1-5 alkyl, C1-5 alkylsulfinylC1-5 alkyl, C1-5 alkylsulfonylC1-5 alkyl, aminoC1-5 alkyl, mono or di-alkylaminoC1-5 alkyl, mono or di-alkylamidoC1-5 alkyl, cyclohexyl, heterocyclylC1-2 alkyl wherein the heterocyclic moiety is selected from pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, 8-aza-bicyclo[3.2.1]octane, silinane, piperazinyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydrothiopyranyl and indolyl, benzyl or naphthylmethyl wherein R_3 is optionally substituted by one or more R_c;

R_c is cyclohexyl, cyclopentyl, indanyl, bicyclo[2.2.1]heptanyl, bicyclo[2.2.2]octanyl, bicyclo[4.1.0]heptanyl, bicyclo[3.1.0]hexanyl, bicyclo[1.1.1]pentanyl, spiro[2.5] octanyl, spiro[3.5] nonyl, spiro[4.5] decanyl,

cubanyl, 1,2,3,4-tetrahydronaphthyl, phenoxy, benzoyl, phenoxycarbonyl, benzoyloxy, phenylthio, fluoro or chloro;

R_9 is hydrogen, C1-5 alkyl, C1-5 alkylene, C1-5 alkoxyC1-5 alkyl, C1-5 alkoxycarbonylC1-5 alkyl, C1-5 alkylthioC1-5 alkyl, C1-5 alkylsulfinylC1-5 alkyl, C1-5 alkylsulfonylC1-5 alkyl, aminoC1-5 alkyl, mono or di-C1-5alkylaminoC1-5 alkyl, mono or di-C1-5 alkylamidoC1-5 alkyl, phenyl, furanyl, thienyl, thiazolyl, imidazolyl, pyridinyl, indolyl or cyano wherein R_9 is optionally substituted by one to two groups of the formula R_e;

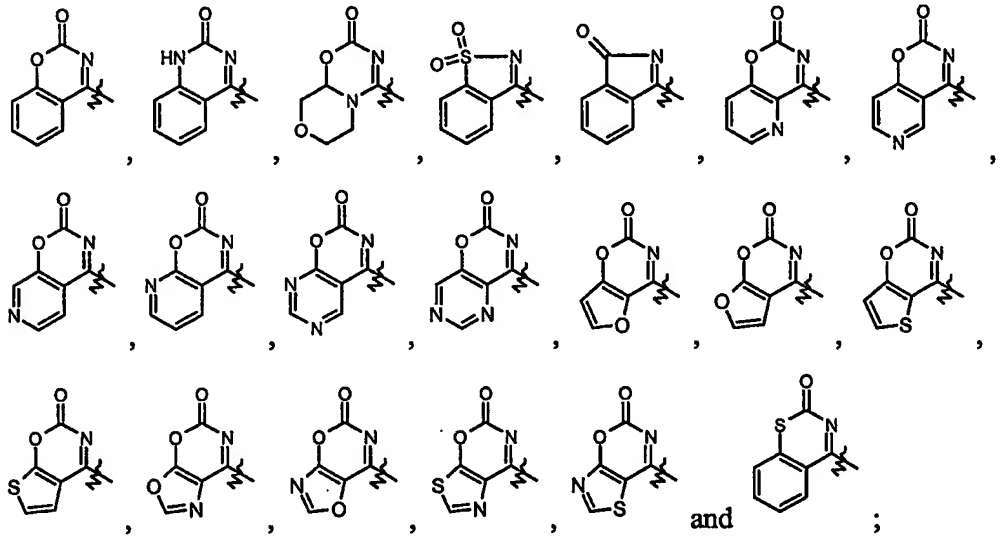
R_e is selected from C1-3 alkyl, C3-6 cycloalkyl, phenyl, naphthyl, benzoyl, furanyl, thienyl, thiazolyl, imidazolyl, pyridinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, indolyl, halogen, hydroxy, oxo, carboxy and cyano, R_e may be further optionally substituted by one or more R_f;

R_f is selected from C1-3 alkyl, phenyl optionally substituted by one or more groups selected from halogen and methyl, heterocyclyl selected from piperidinyl, morpholinyl and piperazinyl; heteroaryl selected from furanyl, thienyl, pyrrolyl and pyridinyl, C1-3 alkoxy, aryloxy, benzoyl, benzyloxy, C1-5 alkoxycarbonyl, C1-5 alkanoyloxy, aroyloxy, carbamoyl wherein the nitrogen atom may be independently mono or di-substituted by C1-5 alkyl or phenyl, C1-5 alkanoylamino, aroylamino, C1-5 alkylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, ureido wherein either nitrogen atom may be independently substituted by C1-5 alkyl or phenyl, C1-5 alkoxycarbonylamino, C1-5 alkylcarbamoyloxy, arylcarbamoyloxy, C1-3 alkylsulfonylamino, arylsulfonylamino, C1-3 alkylaminosulfonyl, arylaminosulfonyl, amino wherein the nitrogen atom may be independently mono or di-substituted by C1-3 alkyl or phenyl, halogen, hydroxy, oxo, nitro, carboxy and cyano;

R_g is selected from C1-3 alkyl, phenyl, C1-3 alkoxycarbonyl, phenoxyoxycarbonyl, benzyloxy, carbamoyl wherein the nitrogen atom may be optionally mono or di-substituted with a group selected from C1-5 alkyl, phenyl and benzyl, halogen, hydroxy, carboxy and cyano.

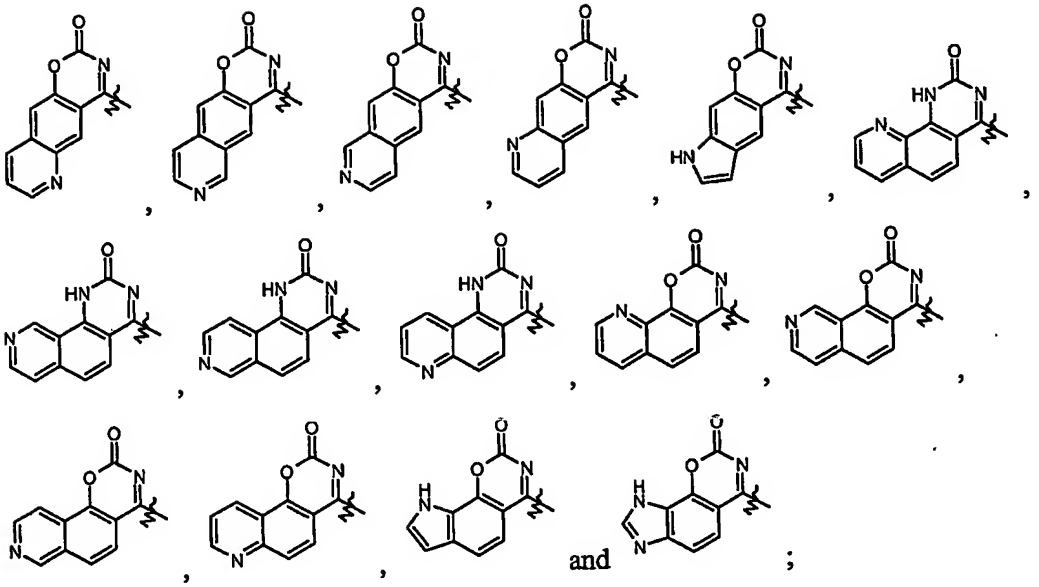
In a further embodiment of the invention, there are provided novel compounds of the formulas (Ia) as described immediately above, and wherein:

R_1 and R_6 of the formula (Ia) form the bicyclic ring selected from:



and ;

or R_1 and R_6 of the formula (Ia) form the tricyclic ring selected from:



wherein each ring is optionally independently substituted by one or two R_7;

R_3 is methyl, ethyl, n-propyl, propenyl, butenyl, i-butenyl, C1-3 alkoxyC1-3 alkyl, C1-3 alkoxycarbonylC1-3 alkyl, C1-3 alkylthioC1-3 alkyl, C1-3 alkylsulfinylC1-3 alkyl, C1-3 alkylsulfonylC1-3 alkyl, aminoC1-3 alkyl, mono or di-C1-3 alkylaminoC1-3 alkyl, mono or di-C1-3 alkylamidoC1-3 alkyl, heterocyclylC1-2 alkyl wherein the heterocyclic moiety is selected from pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, 8-aza-bicyclo[3.2.1]octane, silinane, piperazinyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydrothiopyranyl and indolyl, benzyl or naphthylmethyl wherein R_3 is optionally substituted by one to two R_c;

R_c is methyl, cyclohexyl, cyclopentyl, indanyl, 1,2,3,4-tetrahydronaphthyl, spiro[2.5] octanyl, spiro[3.5] nonyl, spiro[4.5] decanyl, fluoro or chloro;

R_9 is hydrogen, C1-4 alkyl, C1-5 alkylene, C1-3 alkoxyC1-3 alkyl, C1-3 alkoxycarbonylC1-3 alkyl, C1-3 alkylthioC1-3 alkyl, C1-3 alkylsulfinylC1-3 alkyl, C1-3 alkylsulfonylC1-3 alkyl, aminoC1-3 alkyl, mono or di-C1-3 alkylaminoC1-3 alkyl, mono or di-C1-3 alkylamidoC1-3 alkyl, phenyl, furanyl, thienyl, thiazolyl, imidazolyl,

pyridinyl, indolyl or cyano wherein R_9 is optionally substituted by one to two groups of the formula R_e;

R_e is selected from methyl, C3-6 cycloalkyl, phenyl, benzoyl, naphthyl, furanyl, thienyl, thiazolyl, imidazolyl, pyridinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, indolyl, halogen, hydroxy, carboxy and cyano, R_e may be further optionally substituted by one or more R_f;.

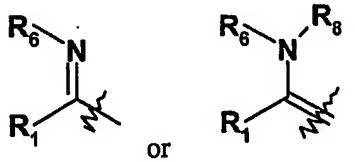
R_f is selected from C1-3 alkyl, phenyl or phenylsulfonyl each optionally substituted by one or more groups selected from halogen or methyl, C1-3 alkoxy, aryloxy, benzoyl, benzyloxy, C1-3 alkoxycarbonyl, carbamoyl wherein the nitrogen atom may be independently mono or di-substituted by C1-3 alkyl or phenyl, C1-5 alkanoylamino, aroylamino, amino wherein the nitrogen atom may be independently mono or di-substituted by C1-3 alkyl or phenyl, halogen, hydroxy, oxo, nitro, carboxy and cyano;

and

R_g is selected from C1-3 alkyl, phenyl, C1-3 alkoxycarbonyl, benzyloxy and carboxy.

In another embodiment of the invention, there are provided novel compounds of the formulas (Ia) or I(b) as described for the broadest generic aspect above and wherein:

R_1 and R_6 remain acyclic:



;

R_1 is a bond, C1-5 alkyl, C1-5 alkoxy, C3-6 cycloalkyl, aryloxy, phenyl, benzyl, naphthyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, furanyl, thienyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl,

indolyl, quinolinyl, benzofuranyl, benzthienyl, benzimidazolyl, benzthiazolyl, benzoxazolyl or amino; wherein R_1 is optionally substituted by one or more R_a;

R_a is a bond, C1-3 alkyl, cyclopropyl, cyclohexyl, phenyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, thienyl, imidazolyl, C1-3 alkoxy, C1-3alkanoyl, C1-3alkanoyloxy, aryloxy, benzyloxy, C1-3 alkoxycarbonyl, aryloxycarbonyl, aroyloxy, carbamoyl wherein the nitrogen atom may be independently mono or di-substituted by C1-3 alkyl, aryl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl or piperazinyl,
or R_a is C1-3 alkanoylamino, aroylamino, C1-3 alkylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, arylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, ureido wherein either nitrogen atom may be independently substituted by C1-3 alkyl, aryl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl or piperazinyl,
or R_a is C1-3 alkoxycarbonylamino, aryloxycarbonylamino, C1-3 alkylcarbamoyloxy, arylcarbamoyloxy, C1-3 alkylsulfonylamino, arylsulfonylamino, C1-3 alkylaminosulfonyl, arylaminosulfonyl, amino wherein the nitrogen atom may be independently mono or di-substituted by C1-3 alkyl, aryl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl or piperazinyl,
or R_a is halogen, hydroxy, oxo, carboxy, cyano, nitro, carboxamide, amidino or guanidino, R_a may be further optionally substituted by one or more R_b;

R_b is methyl, ethyl, n-propyl, i-propyl, cyclopropyl, cyclopentyl, cyclohexyl, phenyl, methoxy, ethoxy, n-propoxy, i-propoxy, phenoxy, benzyloxy, fluoro, chloro, bromo, iodo, hydroxy, oxo, carboxy, cyano, nitro or carboxamide;

R_2 is hydrogen or methyl or ethyl;

R_3 is a bond, hydrogen, C1-10 alkyl wherein one or more carbon atoms are optionally replaced by O, S or N, or R_3 is C2-5alkylene, C3-7 cycloalkyl, heterocyclylC1-5 alkyl

wherein the heterocyclic moiety is selected from pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, 8-aza-bicyclo[3.2.1]octane, silinane, piperazinyl, indolinyl, furanyl, tetrahydrofuranyl, pyranyl, tetrahydropyranyl, tetrahydrothiopyranyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, pyridinyl, pyrimidinyl, pyrazinyl and indolyl, arylC1-3alkyl or aryl wherein R_3 is optionally substituted by one or more R_c;

R_c is C3-7 cycloalkyl, aryl, indanyl, indenyl, bicyclo[2.2.1]heptanyl, bicyclo[2.2.2]octanyl, bicyclo[4.1.0]heptanyl, bicyclo[3.1.0]hexanyl, bicyclo[1.1.1]pentanyl, spiroC8-10 cycloalkyl, cubanyl, 1,2,3,4-tetrahydronaphthyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, indolinyl, furanyl, tetrahydrofuranyl, pyranyl, tetrahydropyranyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, aryloxy, aroyl, aryloxycarbonyl, aroyloxy,
or R_c is aroylamino, arylthio, aryloxycarbonylamino, arylcarbamoyloxy, arylsulfonylamino, arylaminosulfonyl, amino wherein the nitrogen atom may be independently mono or di-substituted by C1-5 alkyl, aryl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, indolinyl, furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl, isoquinolinyl, quinazolinyl or quinoxalinyl,
or R_c is halogen, hydroxy, oxo, carboxy, cyano, nitro, amidino or guanidino, R_c may be further optionally substituted by one or more R_d;
R_d is C1-5 alkyl, C3-6 cycloalkyl, aryl, arylC1-4 alkyl, C1-5 alkoxy, aryloxy, arylC1-5alkoxy, aroyl, halogen, hydroxy, oxo or cyano;

R_4 is hydrogen or methyl;

R_9 is hydrogen, C1-12 alkyl wherein one or more carbon atoms are optionally replaced by O, S or N, C3-7 cycloalkyl, heterocyclyl selected from pyrrolidinyl, piperidinyl,

morpholinyl, thiomorpholinyl, piperazinyl and indolinyl, heteroaryl selected from furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, tetrazolyl, thiadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, indolyl, isoindolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, purinyl, quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, carbazolyl, phenothiazinyl and phenoxazinyl, aryl or cyano, wherein R_9 is optionally substituted by one or more R_e;

R_e is selected from C1-8 alkyl, C3-7 cycloalkyl, aryl, aroyl, heterocyclyl selected from pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl and indolinyl; heteroaryl selected from furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, tetrazolyl, thiadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, indolyl, isoindolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, purinyl, quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, carbazolyl, phenothiazinyl and phenoxazinyl, halogen, hydroxy, oxo, carboxy, cyano, nitro, amidino and guanidino, R_e may be further optionally substituted by one or more R_f;

R_f is selected from C1-8 alkyl, C3-7 cycloalkyl, aryl optionally substituted by one or more groups selected from halogen, methyl or methoxy, heterocyclyl selected from pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl and indolinyl; heteroaryl selected from furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, tetrazolyl, thiadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, indolyl, isoindolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, purinyl, quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, carbazolyl, phenothiazinyl and phenoxazinyl, C1-8 alkoxy, aryloxy, aroyl, arylC1-8alkoxy, C1-8 alkoxycarbonyl, aryloxycarbonyl, C1-8 alkanoyloxy, aroyloxy, carbamoyl wherein the nitrogen atom may be independently mono or di-substituted by C1-8 alkyl, aryl, heterocyclyl selected from

pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl and indolinyl, or heteroaryl selected from furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, tetrazolyl, thiadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, indolyl, isoindolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, purinyl, quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, carbazolyl, phenothiazinyl and phenoxazinyl, C1-8 alkanoylamino, aroylamino, C1-8 alkylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, arylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, ureido wherein either nitrogen atom may be independently substituted by alkyl, aryl, heterocyclyl selected from pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl and indolinyl, or heteroaryl selected from furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, tetrazolyl, thiadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, indolyl, isoindolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, purinyl, quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, carbazolyl, phenothiazinyl and phenoxazinyl, alkoxycarbonylamino, aryloxycarbonylamino, alkylcarbamoyloxy, arylcarbamoyloxy, alkylsulfonylamino, arylsulfonylamino, alkylaminosulfonyl, arylaminosulfonyl, amino wherein the nitrogen atom may be independently mono or di-substituted by alkyl, aryl, heterocyclyl selected from pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl and indolinyl, or heteroaryl selected from furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, tetrazolyl, thiadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, indolyl, isoindolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, purinyl, quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, carbazolyl, phenothiazinyl and phenoxazinyl, halogen, hydroxy, oxo, carboxy, cyano, nitro, amidino and guanidino;

or R_5 and R_9 together with the carbon they are attached form a 3 to 7-membered monocyclic carbocycle or a 7 to 14-membered bicyclic carbocycle optionally bridged, wherein either carbocycle is optionally benzofused and optionally substituted with one or more R_g;

R_g is selected from C1-8 alkyl, aryl, C1-8 alkoxycarbonyl, aryloxycarbonyl, arylC1-8alkoxycarbonyl, carbamoyl wherein the nitrogen atom may be optionally mono or di-substituted with a group selected from C1-8 alkyl, C3-7 cycloalkyl, aryl, arylC1-8alkyl, heterocyclyl selected from pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl and indolinyl, or heteroaryl selected from furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, tetrazolyl, thiadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, indolyl, isoindolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, purinyl, quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, carbazolyl, phenothiazinyl and phenoxazinyl, halogen, hydroxy, carboxy and cyano;

R_6 is

hydroxy, nitrile or

a C1-5 saturated or unsaturated branched or unbranched alkyl optionally partially or fully halogenated wherein one or more C atoms are optionally replaced by O, NH, or $S(O)_2$ and wherein said chain is optionally independently substituted with 1-2 oxo groups, -NH_2, one or more C1-4 alkyl, C3-6 cycloalkyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, indolinyl, pyranyl, thiopyranyl, furanyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl, isoquinolinyl, quinazolinyl, benzoxazolyl or quinoxalinyl;

R_8 is hydrogen, C1-5 alkyl, C3-6 cycloalkyl, aryl, C1-5 alkoxy, aryloxy, benzyloxy each of the aforementioned are optionally halogenated or hydroxy;

and

X is O.

In another embodiment of the invention, there are provided novel compounds of the formula (Ia) or (Ib) as described immediately above, and wherein:

R_1 is a bond, methyl, ethyl, i-propyl, methoxy, ethoxy, cyclopropyl, cyclopentyl, cyclohexyl, phenoxy, phenyl, benzyl, naphthyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, furanyl, thienyl, thiazolyl, imidazolyl, pyridinyl, pyrazinyl or amino; wherein R_1 is optionally substituted by one or more R_a;

R_a is a bond, methyl, ethyl, cyclopropyl, phenyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, thienyl, imidazolyl, methoxy, acetyl, acetoxy, phenoxy, benzyloxy, methoxycarbonyl, phenoxycarbonyl, benzoyloxy, carbamoyl wherein the nitrogen atom may be independently mono or di-substituted by methyl, ethyl or phenyl,
or R_a is acetylamino, benzoylamino, methylthio, phenylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, ureido wherein either nitrogen atom may be independently substituted by methyl, ethyl or phenyl,
or R_a is methoxycarbonylamino, phenoxycarbonylamino, methylcarbamoyloxy, phenylcarbamoyloxy, methylsulfonylamino, phenylsulfonylamino, methylaminosulfonyl, phenylaminosulfonyl, amino wherein the nitrogen atom may be independently mono or di-substituted by methyl or phenyl,
or R_a is fluoro, chloro, bromo, iodo, hydroxy, oxo, carboxy, cyano, nitro or carboxamide, R_a may be further optionally substituted by one or more R_b;

R_b is methyl, cyclopropyl, phenyl, methoxy, phenoxy, benzyloxy, fluoro, chloro, hydroxy, oxo, carboxy or carboxamide;

R_3 is a bond, hydrogen, C1-10 alkyl wherein one or more carbon atoms are optionally replaced by O, S or N, or R_3 is C2-5alkylene, C4-6 cycloalkyl, heterocyclylC1-5 alkyl wherein the heterocyclic moiety is selected from pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, 8-aza-bicyclo[3.2.1]octane, silinane, piperazinyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydrothiopyranyl and indolyl, or arylC1-2alkyl wherein R_3 is optionally substituted by one or more R_c;

R_c is C5-6 cycloalkyl, phenyl, naphthyl, indanyl, bicyclo[2.2.1]heptanyl, bicyclo[2.2.2]octanyl, bicyclo[4.1.0]heptanyl, bicyclo[3.1.0]hexanyl, bicyclo[1.1.1]pentanyl, spiroC8-10 cycloalkyl, cubanyl, 1,2,3,4-tetrahydronaphthyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, indolinyl, furanyl, tetrahydrofuranyl, pyranyl, tetrahydropyranyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, phenoxy, naphthyloxy, benzoyl, phenoxycarbonyl, benzoyloxy, benzoylamino, phenylthio, aryloxycarbonylamino, arylcarbamoyloxy, arylsulfonylamino, arylaminosulfonyl, amino wherein the nitrogen atom may be independently mono or di-substituted by C1-5 alkyl or aryl, or R_c is halogen, hydroxy, oxo, carboxy, cyano, nitro, amidino or guanidino, R_c may be further optionally substituted by one or more R_d;

R_d is C1-3 alkyl, C3-6 cycloalkyl, phenyl, benzyl, C1-3 alkoxy, phenoxy, phenylC1-3alkoxy, benzoyl, halogen, hydroxy, oxo or cyano;

R_5 is hydrogen, C1-8 alkyl, C1-3 alkoxyC1-3 alkyl, C1-8 alkoxy, C1-5phenyl or C1-5naphthyl;

R_9 is hydrogen, C1-12 alkyl wherein one or more carbon atoms are optionally replaced by O, S or N, C3-7 cycloalkyl, heterocyclyl selected from pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl and indolinyl; heteroaryl selected from

furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl, isoquinolinyl, quinazolinyl and quinoxalinyl, aryl or cyano, wherein R_9 is optionally substituted by one or more R_e;

R_e is selected from C1-5 alkyl, C3-7 cycloalkyl, aryl, aroyl, heterocyclyl selected from pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl and indolinyl; heteroaryl selected from furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl, isoquinolinyl, quinazolinyl and quinoxalinyl, halogen, hydroxy, oxo, carboxy, cyano, nitro, amidino and guanidino, R_e may be further optionally substituted by one or more R_f;

R_f is selected from C1-5 alkyl, C3-7 cycloalkyl, aryl optionally substituted by one or more groups selected from halogen, methyl or methoxy, heterocyclyl selected from pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl and indolinyl, heteroaryl selected from furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl, isoquinolinyl, quinazolinyl and quinoxalinyl, C1-5 alkoxy, aryloxy, aroyl, arylC1-5alkoxy, C1-5 alkoxycarbonyl, aryloxycarbonyl, C1-5 alkanoyloxy, aroyloxy, carbamoyl wherein the nitrogen atom may be independently mono or di-substituted by C1-5 alkyl, aryl, heterocyclyl selected from pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl and indolinyl or heteroaryl selected from furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl, isoquinolinyl, quinazolinyl and quinoxalinyl, C1-5 alkanoylamino, aroylamino, C1-5 alkylthio wherein the sulfur atom

may be oxidized to a sulfoxide or sulfone, arylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, ureido wherein either nitrogen atom may be independently substituted by C1-5 alkyl, aryl, heterocyclyl selected from pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl and indolinyl, or heteroaryl selected from furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl, isoquinolinyl, quinazolinyl and quinoxalinyl, C1-5 alkoxycarbonylamino, aryloxycarbonylamino, C1-5 alkylcarbamoyloxy, arylcarbamoyloxy, C1-5 alkylsulfonylamino, arylsulfonylamino, C1-5 alkylaminosulfonyl, arylaminosulfonyl, amino wherein the nitrogen atom may be independently mono or di-substituted by C1-5 alkyl, aryl, heterocyclyl selected from pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl and indolinyl, or heteroaryl selected from furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl, isoquinolinyl, quinazolinyl and quinoxalinyl, halogen, hydroxy, oxo, carboxy, cyano, nitro, amidino and guanidino;

or R_5 and R_9 together with the carbon they are attached form a 3 to 7-membered monocyclic carbocycle or a 7 to 14-membered bicyclic carbocycle optionally bridged, wherein either carbocycle is optionally benzofused and optionally substituted with one or more R_g;

R_g is selected from C1-5 alkyl, aryl, C1-5 alkoxycarbonyl, aryloxycarbonyl, arylC1-5alkoxycarbonyl, carbamoyl wherein the nitrogen atom may be optionally mono or di-substituted with a group selected from C1-5 alkyl, C3-7 cycloalkyl, aryl, arylC1-5alkyl, heterocyclyl selected from pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl and indolinyl, or heteroaryl selected from furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl,

benzofuranyl; benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl, isoquinolinyl, quinazolinyl and quinoxalinyl, halogen, hydroxy, carboxy and cyano;

R_6 is
nitrile or
a C1-5 saturated or unsaturated branched or unbranched alkyl optionally partially or fully halogenated wherein one or more C atoms are optionally replaced by O, NH, or $S(O)_2$ and wherein said chain is optionally independently substituted with oxo, $-NH_2$, C3-6 cycloalkyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, pyridinyl, pyrimidinyl or pyrazinyl; and

R_8 is hydrogen, C1-3 alkyl, C3-6 cycloalkyl, phenyl, C1-3 alkoxy, benzyloxy each of the aforementioned are optionally halogenated or hydroxy.

In yet another embodiment of the invention, there are provided novel compounds of the formula (Ia) or formula (Ib) as described immediately above, and wherein:

R_1 is a bond, methyl, ethyl, i-propyl, methoxy, cyclopropyl, cyclohexyl, phenoxy, phenyl, benzyl, naphthyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, furanyl, thienyl, thiazolyl, imidazolyl, pyridinyl, pyrazinyl or amino; wherein R_1 is optionally substituted by one or more R_a;

R_a is methyl, phenyl, thienyl, methoxy, acetyl, acetoxy, phenoxy, benzyloxy, methoxycarbonyl, benzoyloxy, carbamoyl wherein the nitrogen atom may be independently mono or di-substituted by methyl or phenyl,
or R_a is acetylamino, methylthio, phenylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, ureido wherein either nitrogen atom may be independently substituted by methyl or phenyl,

or R_a is methoxycarbonylamino, methylcarbamoyloxy, phenylcarbamoyloxy, methylsulfonylamino, phenylsulfonylamino, amino wherein the nitrogen atom may be independently mono or di-substituted by methyl or phenyl, or R_a is fluoro, chloro, hydroxy, oxo, carboxy, cyano or carboxamide;

R_3 is a bond, C1-10 alkyl wherein one or more carbon atoms are optionally replaced by O, S or N, or R_3 is C2-4alkylene, C5-6 cycloalkyl, heterocyclylC1-3 alkyl wherein the heterocyclic moiety is selected from pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, 8-aza-bicyclo[3.2.1]octane, silinane, piperazinyl, tetrahydrofuranyi, tetrahydropyranyl, tetrahydrothiopyranyl and indolyl, benzyl or naphthylmethyl wherein R_3 is optionally substituted by one or more R_c;

R_c is C5-6 cycloalkyl, phenyl, naphthyl, indanyl, bicyclo[2.2.1]heptanyl, bicyclo[2.2.2]octanyl, bicyclo[4.1.0]heptanyl, bicyclo[3.1.0]hexanyl, bicyclo[1.1.1]pentanyl, spiroC8-10 cycloalkyl, cubanyl, 1,2,3,4-tetrahydronaphthyl, furanyl, tetrahydropyranyl, thienyl, oxazolyl, thiazolyl, imidazolyl, pyrimidinyl, indolyl, benzofuranyl, benzothienyl, benzthiazolyl, phenoxy, naphthyloxy, benzoyl, phenoxycarbonyl, benzoyloxy, benzoylamino, phenylthio, phenoxycarbonylamino, arylcarbamoyloxy, phenylsulfonylamino, phenylaminosulfonyl, amino wherein the nitrogen atom may be independently mono or di-substituted by C1-3 alkyl or phenyl, or R_c is halogen, hydroxy, oxo, carboxy or cyano, R_c may be further optionally substituted by one or more R_d;

R_d is methyl, cyclopropyl, cyclohexyl, phenyl, benzyl, methoxy, phenoxy, benzyloxy, benzoyl, fluoro, chloro, oxo or cyano;

R_5 is hydrogen, C1-5 alkyl, C1-3 alkoxyC1-3 alkyl, benzyl or phenethyl;

R_9 is hydrogen, C1-12 alkyl wherein one or more carbon atoms are optionally replaced by O, S or N, C3-7 cycloalkyl, heterocyclyl selected from pyrrolidinyl, piperidinyl,

morpholinyl, thiomorpholinyl, piperazinyl and indolinyl; heteroaryl selected from furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl, isoquinolinyl, quinazolinyl and quinoxalinyl, phenyl, naphthyl or cyano, wherein R_9 is optionally substituted by one or more R_e;.

R_e is selected from C1-5 alkyl, C3-7 cycloalkyl, phenyl, naphthyl, aroyl, heterocyclyl selected from pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl and indolinyl; heteroaryl selected from furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl, isoquinolinyl, quinazolinyl and quinoxalinyl, C1-5 alkoxy, aryloxy, aroyl, arylC1-5alkoxy, heteroarylC1-5alkoxy, C1-5 alkoxycarbonyl, aryloxycarbonyl, C1-5 alkanoyloxy, aroyloxy, carbamoyl wherein the nitrogen atom may be independently mono or di-substituted by C1-5 alkyl, aryl, heterocyclyl selected from piperidinyl, morpholinyl and piperazinyl or heteroaryl selected from furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl and isoquinolinyl, C1-5 alkanoylamino, aroylamino, C1-5 alkylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, arylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, arylC1-5 alkylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, ureido wherein either nitrogen atom may be independently substituted by C1-5 alkyl, aryl, heterocyclyl selected from piperidinyl, morpholinyl and piperazinyl or heteroaryl selected from furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl and isoquinolinyl, halogen, hydroxy, oxo, nitro, carboxy and cyano, R_e may be further optionally substituted by one or more R_f;

R_f is selected from C1-5 alkyl, C3-7 cycloalkyl, phenyl optionally substituted by one or more groups selected from halogen, methyl or methoxy, naphthyl optionally substituted by one or more groups selected from halogen, methyl or methoxy, heterocyclyl selected from pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl and indolinyl; heteroaryl selected from furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl, isoquinolinyl, quinazolinyl and quinoxalinyl, C1-5 alkoxy, aryloxy, arylC1-5alkoxy, C1-5 alkoxycarbonyl, aryloxycarbonyl, C1-5 alkanoyloxy, aroyloxy, carbamoyl wherein the nitrogen atom may be independently mono or di-substituted by C1-5 alkyl, aryl, heterocyclyl selected from piperidinyl, morpholinyl and piperazinyl or heteroaryl selected from furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl and isoquinolinyl, C1-5 alkanoylamino, aroylamino, C1-5 alkylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, arylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, ureido wherein either nitrogen atom may be independently substituted by C1-5 alkyl, aryl, heterocyclyl selected from piperidinyl, morpholinyl and piperazinyl or heteroaryl selected from furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl and isoquinolinyl, C1-5 alkoxycarbonylamino, aryloxycarbonylamino, C1-5 alkylcarbamoyloxy, arylcarbamoyloxy, C1-5 alkylsulfonylamino, arylsulfonylamino, C1-5 alkylaminosulfonyl, arylaminosulfonyl, amino wherein the nitrogen atom may be independently mono or di-substituted by C1-5 alkyl, aryl, heterocyclyl selected from pyrrolidinyl, piperidinyl, morpholinyl and piperazinyl or heteroaryl selected from furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, indolyl, benzofuranyl, benzothienyl,

benzimidazolyl, benzthiazolyl, quinolinyl and isoquinolinyl, halogen, hydroxy, oxo, carboxy and cyano;

or R_5 and R_9 together with the carbon they are attached form a 3 to 7-membered monocyclic carbocycle or a 7 to 14-membered bicyclic carbocycle optionally bridged, wherein either carbocycle is optionally benzofused and optionally substituted with one or more R_g;

R_g is selected from C1-5 alkyl, phenyl, naphthyl, C1-5 alkoxycarbonyl, aryloxycarbonyl, arylC1-3alkoxycarbonyl, carbamoyl wherein the nitrogen atom may be optionally mono or di-substituted with a group selected from C1-5 alkyl, C3-6 cycloalkyl, phenyl, naphthyl, arylC1-3alkyl, heterocyclyl selected from pyrrolidinyl, piperidinyl, morpholinyl and piperazinyl or heteroaryl selected from furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl and isoquinolinyl, halogen, hydroxy, carboxy and cyano;

R_6 is
nitrile or
a C1-5 saturated or unsaturated branched or unbranched alkyl optionally partially or fully halogenated wherein one or more C atoms are optionally replaced by O, NH, or $S(O)_2$ and wherein said chain is optionally independently substituted with oxo, $-NH_2$, C3-6 cycloalkyl, morpholinyl or piperazinyl; and

R_8 is hydrogen, C1-3 alkyl, C1-3 alkoxy or hydroxy.

In yet still another embodiment of the invention, there are provided novel compounds of the formulas (Ia) or (Ib) as described immediately above, and wherein:

R_1 is i-propyl, benzyloxy, cyclohexyl, phenyl, 4-(acetylamino)-phenyl, 4-(methanesulfonylamino)-phenyl, 4-methoxyphenyl, 3-phenoxyphenyl, 4-chlorophenyl, 4-fluorophenyl, 2-fluorophenyl, 2-fluoro-4-chlorophenyl, naphthyl, thienylmethyl, piperidinyl, morpholinyl, pyrrolidinyl, piperazinyl, furanyl, thienyl, 5-chlorothienyl, pyridin-4-yl, pyrazinyl, methylamino, ethylamino, dimethylamino or diethylamino;

R_3 is a bond, C1-10 alkyl wherein one or more carbon atoms are optionally replaced by O, S or N, or R_3 is C2-4alkylene, C5-6 cycloalkyl, heterocyclylC1-2 alkyl wherein the heterocyclic moiety is selected from pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, 8-aza-bicyclo[3.2.1]octane, silinane, piperazinyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydrothiopyranyl and indolyl, benzyl or naphthylmethyl wherein R_3 is optionally substituted by one or more R_c;

R_c is C5-6 cycloalkyl, indanyl, bicyclo[2.2.1]heptanyl, bicyclo[2.2.2]octanyl, bicyclo[4.1.0]heptanyl, bicyclo[3.1.0]hexanyl, bicyclo[1.1.1]pentanyl, spiroC8-10 cycloalkyl, cubanyl, 1,2,3,4-tetrahydronaphthyl, thienyl, oxazolyl, thiazolyl, indolyl, benzofuranyl, benzothienyl, benzthiazolyl, phenoxy, benzoyl, phenoxycarbonyl, benzoyloxy, benzoylamino, phenylthio, phenoxycarbonylamino, phenylcarbamoyloxy, phenylsulfonylamino, phenylaminosulfonyl, amino wherein the nitrogen atom may be independently mono or di-substituted by methyl, ethyl or phenyl,
or R_c is fluoro, chloro or oxo, R_c may be further optionally substituted by one or more R_d;

R_d is methyl, cyclopropyl, phenyl, methoxy, fluoro, chloro or oxo;

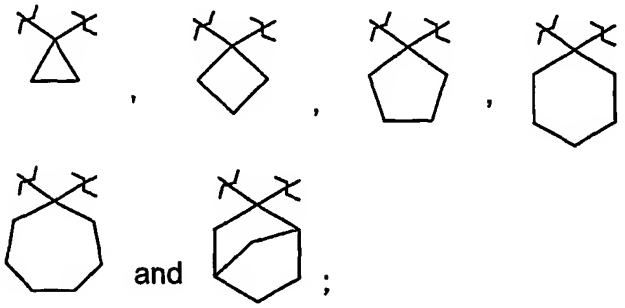
R_9 is hydrogen, C1-12 alkyl wherein one or more carbon atoms are optionally replaced by O, S or N, C3-6 cycloalkyl, phenyl or cyano, wherein R_9 is optionally substituted by one or more R_c;

R_e is selected from C1-3 alkyl, C3-6 cycloalkyl, phenyl, naphthyl, aroyl, heterocyclyl selected from pyrrolidinyl, piperidinyl, morpholinyl, thio morpholinyl and piperazinyl; heteroaryl selected from furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl and isoquinolinyl, C1-5 alkoxy, aryloxy, aroyl, arylC1-3alkoxy, heteroarylC1-3alkoxy, C1-5 alkoxycarbonyl, aryloxycarbonyl, C1-5 alkanoyloxy, aroyloxy, carbamoyl wherein the nitrogen atom may be independently mono or di-substituted by C1-5 alkyl, phenylor heteroaryl selected from furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl and indolyl, C1-5 alkanoylamino, aroylamino, C1-3 alkylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, arylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, arylC1-3alkylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, ureido wherein either nitrogen atom may be independently substituted by C1-5 alkyl or phenyl, C1-5 alkoxycarbonylamino, C1-5 alkylsulfonylamino, arylsulfonylamino, amino wherein the nitrogen atom may be independently mono or di-substituted by C1-5 alkyl, phenyl, naphthyl, heterocyclyl selected from piperidinyl, morpholinyl and piperazinyl or heteroaryl selected from furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, indolyl, halogen, hydroxy, oxo, nitro, carboxy and cyano, R_e may be further optionally substituted by one or more R_f;

R_f is selected from C1-3 alkyl, C5-6 cycloalkyl, phenyl optionally substituted by one or more groups selected from halogen or methyl, heterocyclyl selected from pyrrolidinyl, piperidinyl, morpholinyl and piperazinyl, heteroaryl selected from furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, pyrazinyl and indolyl, C1-5 alkoxy, aryloxy, arylC1-3alkoxy, C1-5 alkoxycarbonyl, aryloxycarbonyl, C1-5 alkanoyloxy, aroyloxy, carbamoyl wherein the nitrogen atom may be independently mono or di-substituted by C1-5 alkyl or aryl, C1-5 alkanoylamino, aroylamino, C1-5 alkylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, arylthio wherein the sulfur atom may

be oxidized to a sulfoxide or sulfone, ureido wherein either nitrogen atom may be independently substituted by C1-5 alkyl or aryl, C1-5 alkoxycarbonylamino, aryloxycarbonylamino, C1-5 alkylcarbamoyloxy, arylcarbamoyloxy, C1-5 alkylsulfonylamino, arylsulfonylamino, C1-5 alkylaminosulfonyl, arylaminosulfonyl, amino wherein the nitrogen atom may be independently mono or di-substituted by C1-5 alkyl or aryl, halogen, hydroxy, oxo, carboxy and cyano;

or R_5 and R_9 together with the carbon they are attached form a carbocyclic ring selected from :



each carbocyclic ring being optionally benzofused and optionally substituted with one or more R_g;

R_g is selected from C1-5 alkyl, phenyl, C1-5 alkoxycarbonyl, aryloxycarbonyl, arylC1-3alkoxycarbonyl, carbamoyl wherein the nitrogen atom may be optionally mono or di-substituted with C1-5 alkyl, C3-6 cycloalkyl, phenyl, naphthyl or arylC1-3alkyl; halogen, hydroxy, carboxy and cyano;

R_6 is C3-6 cycloalkyloxycarbonyl, acetyl, C1-3alkylaminocarbonyl or C1-3alkoxycarbonyl; and

R_8 is hydrogen, C1-3 alkyl or C1-3 alkoxy.

In yet a further embodiment of the invention, there are provided novel compounds of the formulas (Ia) or (Ib) as described immediately above, and wherein:

R_1 is morpholin-4-yl, p-fluorophenyl or p-methoxyphenyl;

R_3 is a bond, methyl, ethyl, n-propyl, propenyl, butenyl, i-butenyl, C1-5 alkoxyC1-5 alkyl, C1-5 alkoxycarbonylC1-5 alkyl, C1-5 alkylthioC1-5 alkyl, C1-5 alkylsulfinylC1-5 alkyl, C1-5 alkylsulfonylC1-5 alkyl, aminoC1-5 alkyl, mono or di-alkylaminoC1-5 alkyl, mono or di-alkylamidoC1-5 alkyl, cyclohexyl, heterocyclylC1-2 alkyl wherein the heterocyclic moiety is selected from pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, 8-aza-bicyclo[3.2.1]octane, silinane, piperazinyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydrothiopyranyl and indolyl, benzyl or naphthylmethyl wherein R_3 is optionally substituted by one or more R_c;

R_c is cyclohexyl, cyclopentyl, indanyl, bicyclo[2.2.1]heptanyl, bicyclo[2.2.2]octanyl, bicyclo[4.1.0]heptanyl, bicyclo[3.1.0]hexanyl, bicyclo[1.1.1]pentanyl, spiro[2.5] octanyl, spiro[3.5] nonyl, spiro[4.5] decanyl, cubanyl, 1,2,3,4-tetrahydronaphthyl, phenoxy, benzoyl, phenoxycarbonyl, benzoyloxy, phenylthio, fluoro or chloro;

R_9 is hydrogen, C1-5 alkyl, C1-5 alkylene, C1-5 alkoxyC1-5 alkyl, C1-5 alkoxycarbonylC1-5 alkyl, C1-5 alkylthioC1-5 alkyl, C1-5 alkylsulfinylC1-5 alkyl, C1-5 alkylsulfonylC1-5 alkyl, aminoC1-5 alkyl, mono or di-C1-5alkylaminoC1-5 alkyl, mono or di-C1-5 alkylamidoC1-5 alkyl, phenyl, furanyl, thienyl, thiazolyl, imidazolyl, pyridinyl, indolyl or cyano wherein R_9 is optionally substituted by one to two groups of the formula R_e;

R_e is selected from C1-3 alkyl, C3-6 cycloalkyl, phenyl, naphthyl, benzoyl, furanyl, thienyl, thiazolyl, imidazolyl, pyridinyl, piperidinyl, piperazinyl,

morpholinyl, thiomorpholinyl, indolyl, halogen, hydroxy, oxo, carboxy and cyano, R_e may be further optionally substituted by one or more R_f;

R_f is selected from C1-3 alkyl, phenyl optionally substituted by one or more groups selected from halogen and methyl, heterocyclyl selected from piperidinyl, morpholinyl and piperazinyl; heteroaryl selected from furanyl, thienyl, pyrrolyl and pyridinyl, C1-3 alkoxy, aryloxy, benzoyl, benzyloxy, C1-5 alkoxycarbonyl, C1-5 alkanoyloxy, aroyloxy, carbamoyl wherein the nitrogen atom may be independently mono or di-substituted by C1-5 alkyl or phenyl, C1-5 alkanoylamino, aroylamino, C1-5 alkylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, ureido wherein either nitrogen atom may be independently substituted by C1-5 alkyl or phenyl, C1-5 alkoxycarbonylamino, C1-5 alkylcarbamoyloxy, arylcarbamoyloxy, C1-3 alkylsulfonylamino, arylsulfonylamino, C1-3 alkylaminosulfonyl, arylaminosulfonyl, amino wherein the nitrogen atom may be independently mono or di-substituted by C1-3 alkyl or phenyl, halogen, hydroxy, oxo, nitro, carboxy and cyano;

R_g is selected from C1-3 alkyl, phenyl, C1-3 alkoxycarbonyl, phenoxyoxycarbonyl, benzyloxy, carbamoyl wherein the nitrogen atom may be optionally mono or di-substituted with a group selected from C1-5 alkyl, phenyl and benzyl, halogen, hydroxy, carboxy and cyano;

R_6 is C3-6 cycloalkyloxycarbonyl, acetyl, ethylaminocarbonyl or ethoxycarbonyl; and

R_8 is hydrogen.

In a further embodiment of the invention, there are provided novel compounds of the formulas (Ia) or (Ib) as described immediately above, and wherein:

R_3 is methyl, ethyl, n-propyl, propenyl, butenyl, i-butenyl, C1-3 alkoxyC1-3 alkyl, C1-3 alkoxycarbonylC1-3 alkyl, C1-3 alkylthioC1-3 alkyl, C1-3 alkylsulfinylC1-3 alkyl, C1-3

alkylsulfonylC1-3 alkyl, aminoC1-3 alkyl, mono or di-C1-3 alkylaminoC1-3 alkyl, mono or di-C1-3 alkylamidoC1-3 alkyl, heterocyclylC1-2 alkyl wherein the heterocyclic moiety is selected from pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, 8-aza-bicyclo[3.2.1]octane, silinane, piperazinyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydrothiopyranyl and indolyl, benzyl or naphthylmethyl wherein R_3 is optionally substituted by one to two R_c;

R_c is methyl, cyclohexyl, cyclopentyl, indanyl, 1,2,3,4-tetrahydronaphthyl, spiro[2.5] octanyl, spiro[3.5] nonyl, spiro[4.5] decanyl, fluoro or chloro;

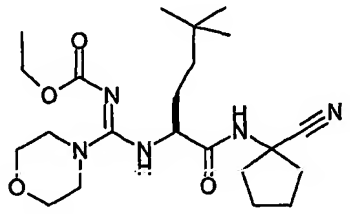
R_9 is hydrogen, C1-4 alkyl, C1-5 alkylene, C1-3 alkoxyC1-3 alkyl, C1-3 alkoxycarbonylC1-3 alkyl, C1-3 alkylthioC1-3 alkyl, C1-3 alkylsulfinylC1-3 alkyl, C1-3 alkylsulfonylC1-3 alkyl, aminoC1-3 alkyl, mono or di-C1-3 alkylaminoC1-3 alkyl, mono or di-C1-3 alkylamidoC1-3 alkyl, phenyl, furanyl, thienyl, thiazolyl, imidazolyl, pyridinyl, indolyl or cyano wherein R_9 is optionally substituted by one to two groups of the formula R_e;

R_e is selected from methyl, C3-6 cycloalkyl, phenyl, benzoyl, naphthyl, furanyl, thienyl, thiazolyl, imidazolyl, pyridinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, indolyl, halogen, hydroxy, carboxy and cyano, R_e may be further optionally substituted by one or more R_f;.

R_f is selected from C1-3 alkyl, phenyl or phenylsulfonyl each optionally substituted by one or more groups selected from halogen or methyl, C1-3 alkoxy, aryloxy, benzoyl, benzyloxy, C1-3 alkoxycarbonyl, carbamoyl wherein the nitrogen atom may be independently mono or di-substituted by C1-3 alkyl or phenyl, C1-5 alkanoylamino, aroylamino, amino wherein the nitrogen atom may be independently mono or di-substituted by C1-3 alkyl or phenyl, halogen, hydroxy, oxo, nitro, carboxy and cyano;

R_g is selected from C1-3 alkyl, phenyl, C1-3 alkoxycarbonyl, benzyloxy and carboxy.

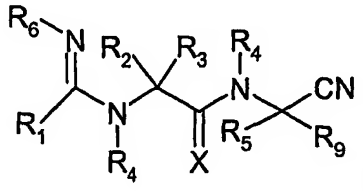
Further compounds of Formula (Ia), made up of components A, B, and C are provided in Tables I & II below. Any and all combinations of A, B, and C components within the structural limitations of Formula (Ia), comprise a compound of the invention, and their pharmaceutically acceptable derivatives. For example, the compound:



would represent the combination of A24,B32,C4.

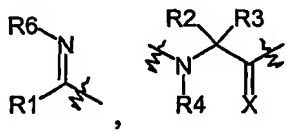
These compounds can be synthesized by the General schemes, methods described in the experimental section of this document and analogous methods known to those skilled in the art without undue experimentation. Preferred compounds will possess desirable inhibition activity of Cathepsin S in a cell based assay as described in Riese, R.J. et al., Immunity, 1996, 4, 357-366, incorporated herein by reference.

FORMULA (Ia)

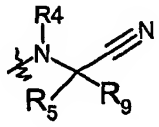


(Ia)

wherein for the Formula (Ia), the components

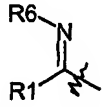
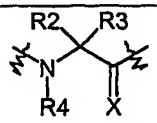
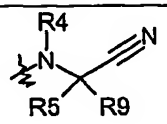
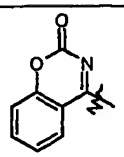
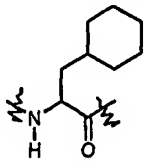
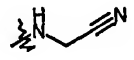
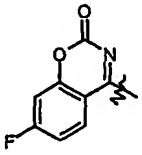
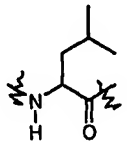
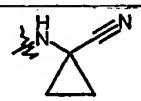
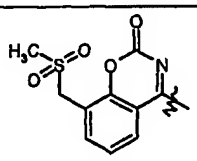
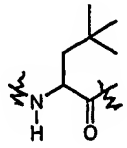
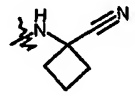
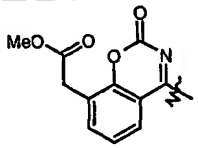
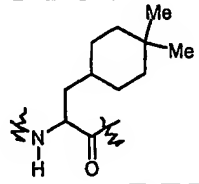
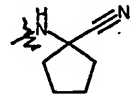
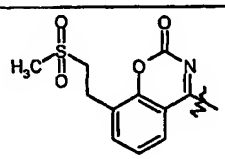
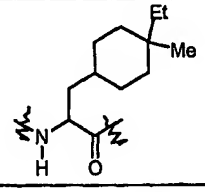
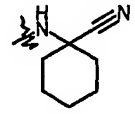
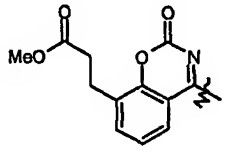
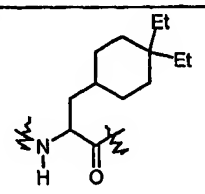
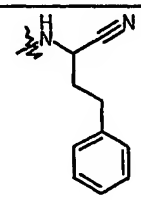
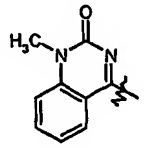
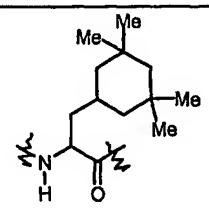
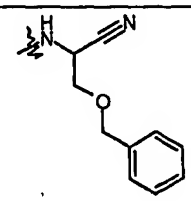


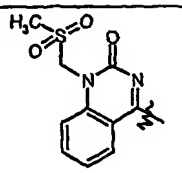
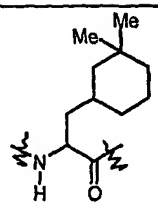
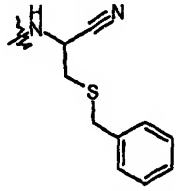
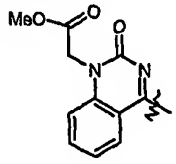
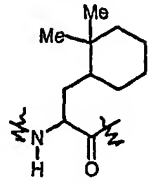
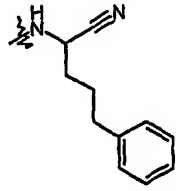
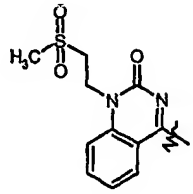
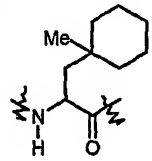
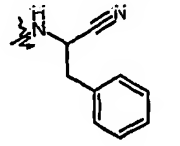
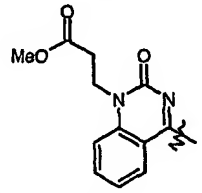
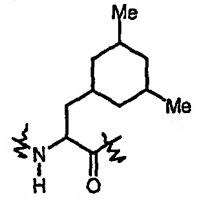
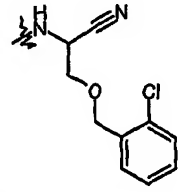
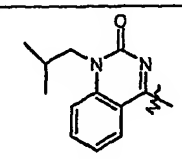
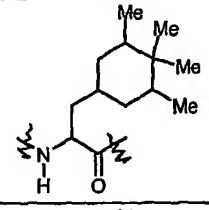
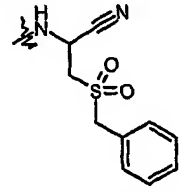
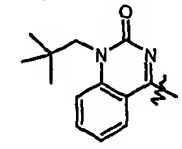
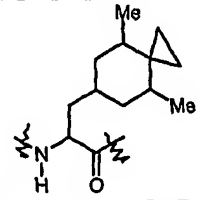
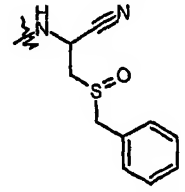
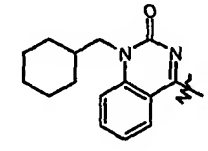
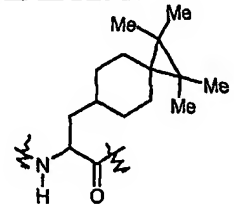
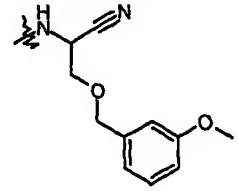
and

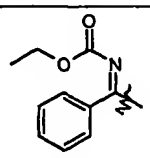
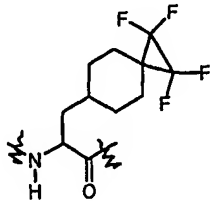
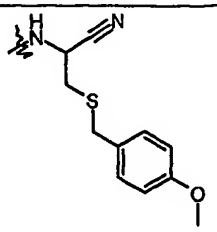
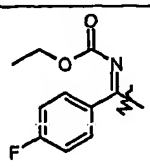
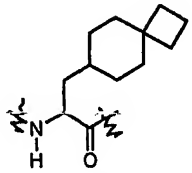
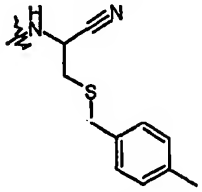
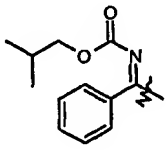
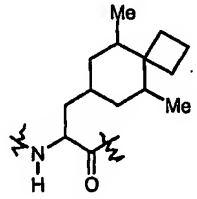
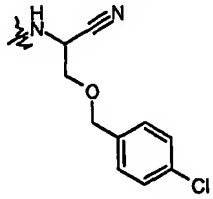
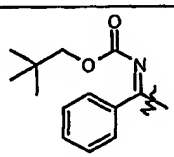
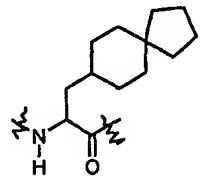
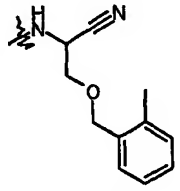
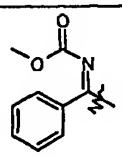
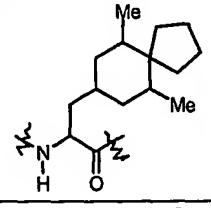
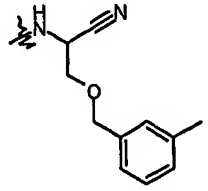
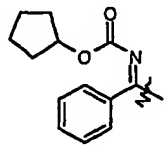
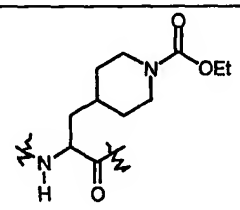
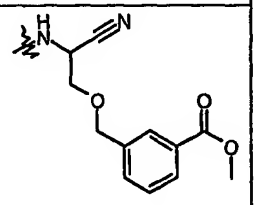


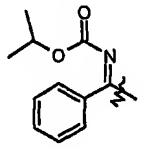
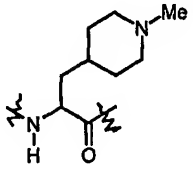
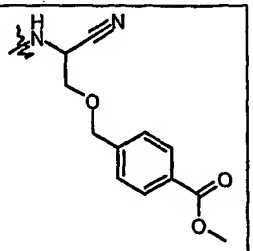
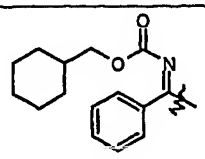
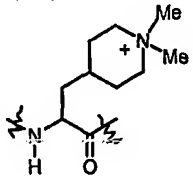
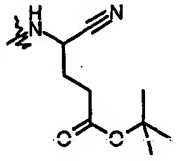
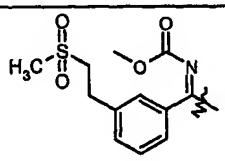
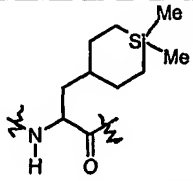
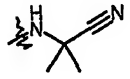
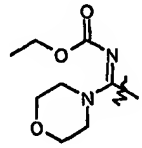
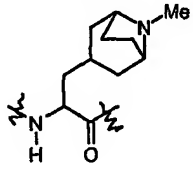
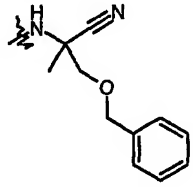
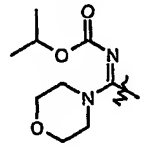
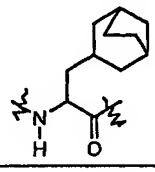
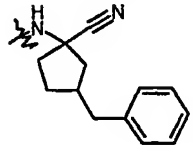
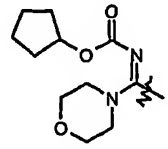
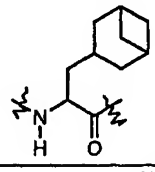
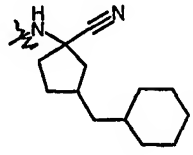
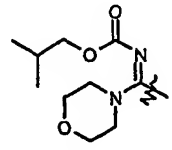
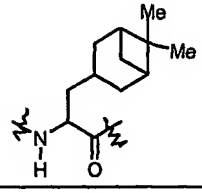
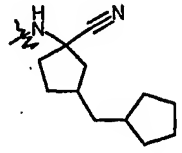
are chosen from any combination of A, B and C as follows:

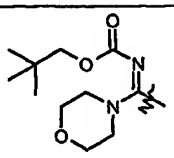
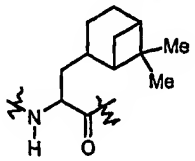
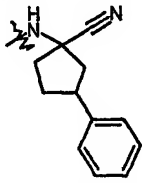
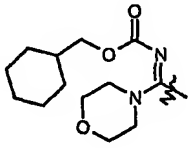
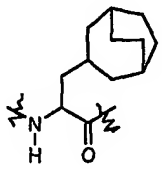
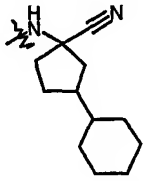
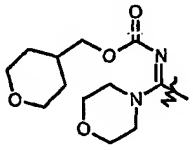
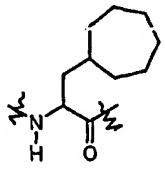
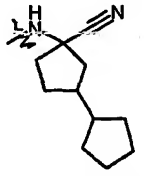
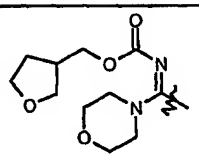
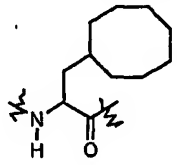
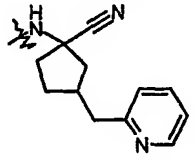
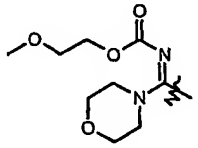
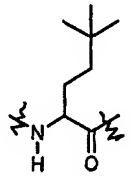
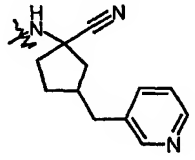
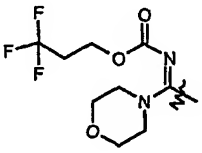
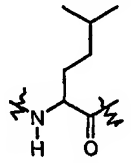
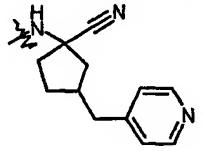
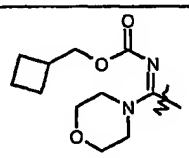
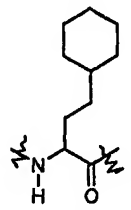
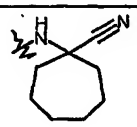
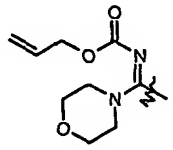
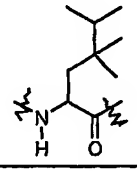
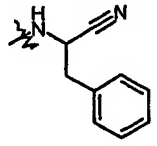
TABLE I

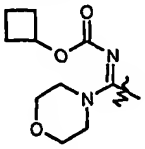
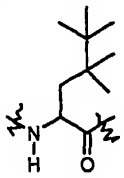
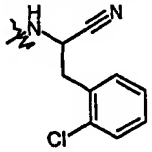
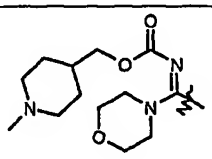
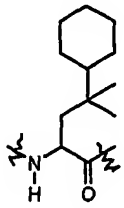
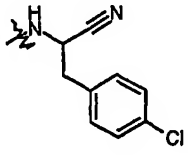
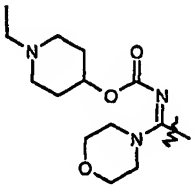
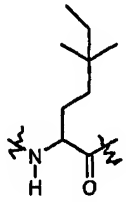
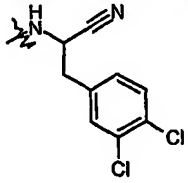
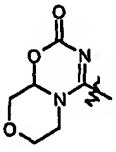
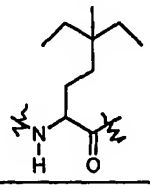
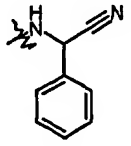
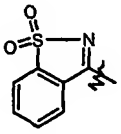
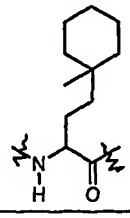
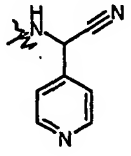
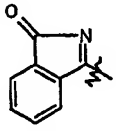
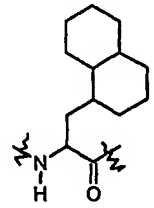
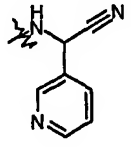
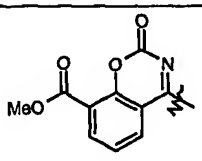
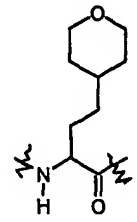
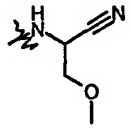
A		B		C	
					
A1		B1		C1	
A2		B2		C2	
A3		B3		C3	
A4		B4		C4	
A5		B5		C5	
A6		B6		C6	
A7		B7		C7	

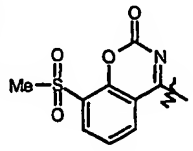
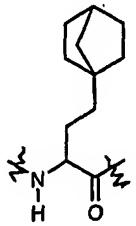
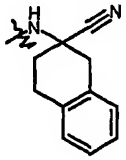
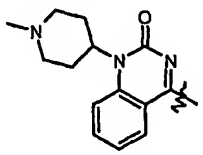
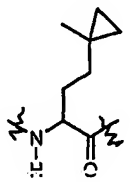
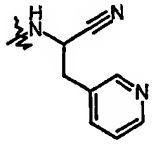
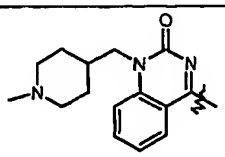
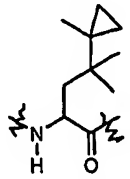
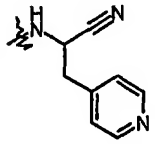
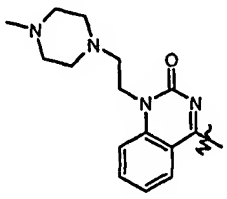
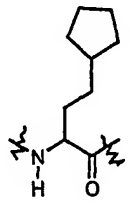
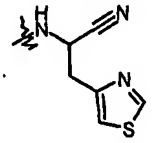
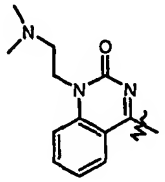
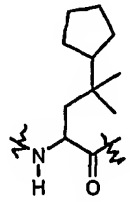
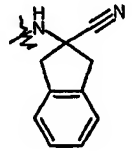
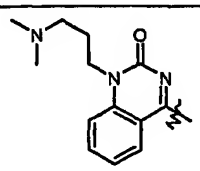
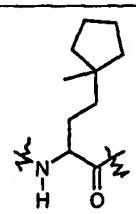
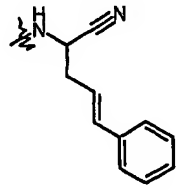
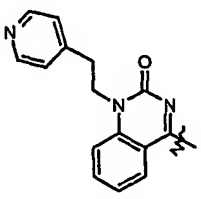
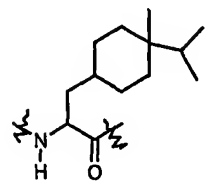
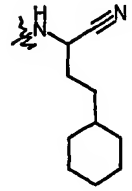
A8		B8		C8	
A9		B9		C9	
A10		B10		C10	
A11		B11		C11	
A12		B12		C12	
A13		B13		C13	
A14		B14		C14	

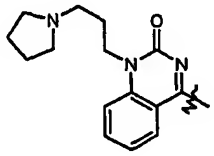
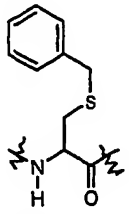
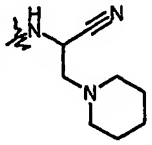
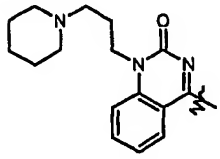
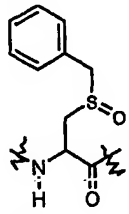
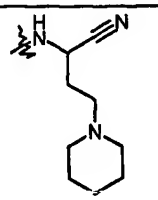
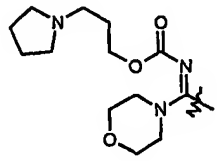
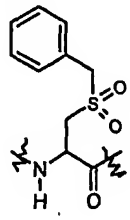
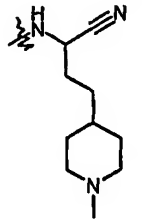
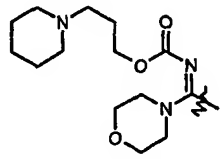
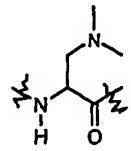
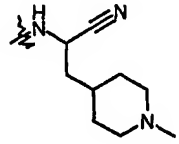
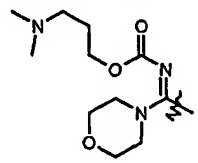
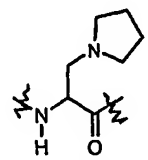
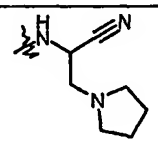
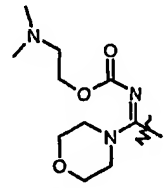
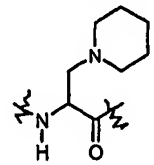
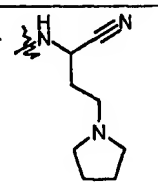
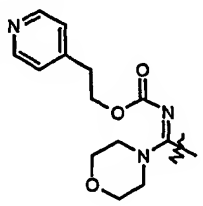
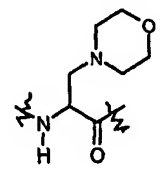
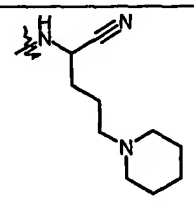
A15		B15		C15	
A16		B16		C16	
A17		B17		C17	
A18		B18		C18	
A19		B19		C19	
A20		B20		C20	

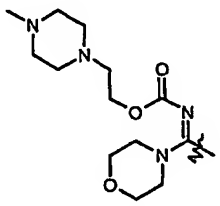
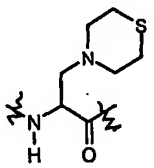
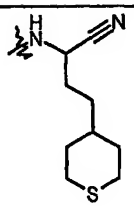
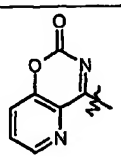
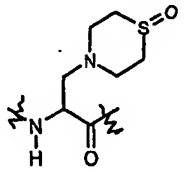
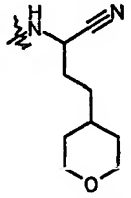
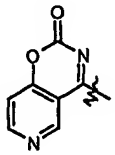
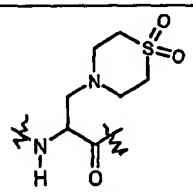
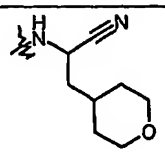
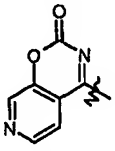
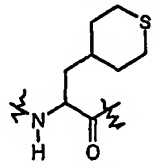
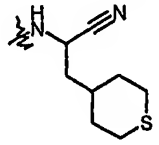
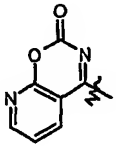
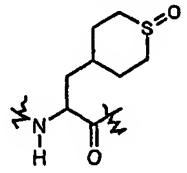
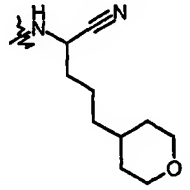
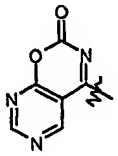
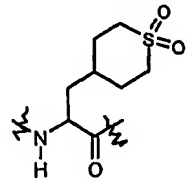
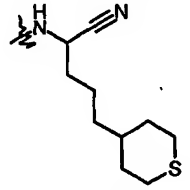
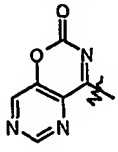
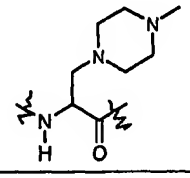
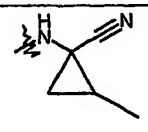
A21		B21		C21	
A22		B22		C22	
A23		B23		C23	
A24		B24		C24	
A25		B25		C25	
A26		B26		C26	
A27		B27		C27	

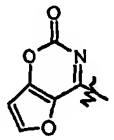
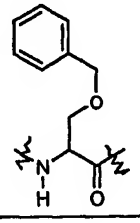
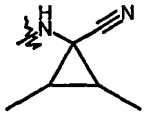
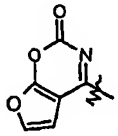
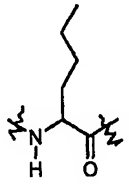
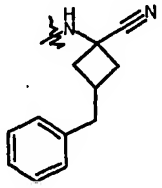
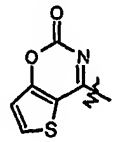
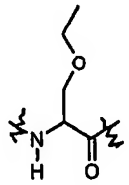
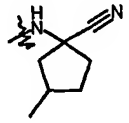
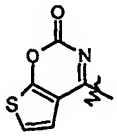
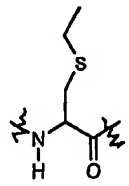
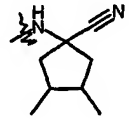
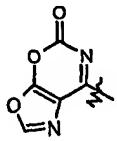
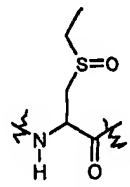
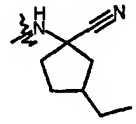
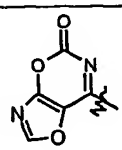
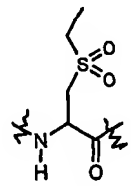
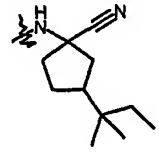
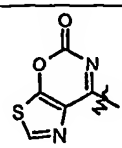
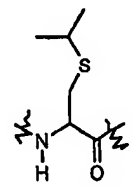
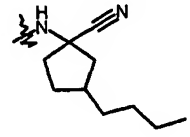
A28		B28		C28	
A29		B29		C29	
A30		B30		C30	
A31		B31		C31	
A32		B32		C32	
A33		B33		C33	
A34		B34		C34	
A35		B35		C35	

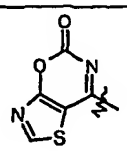
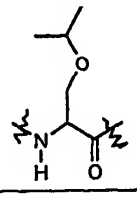
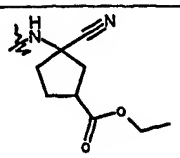
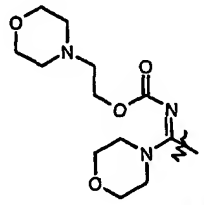
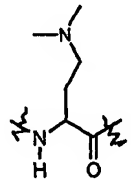
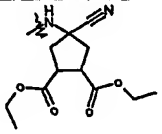
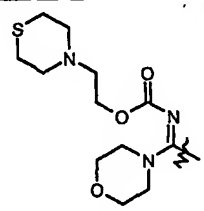
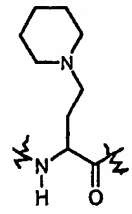
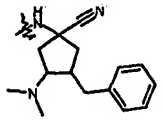
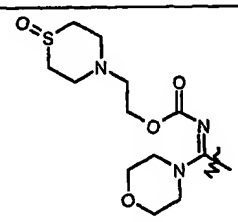
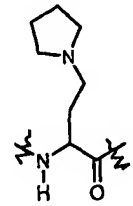
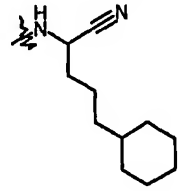
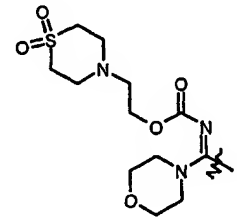
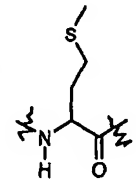
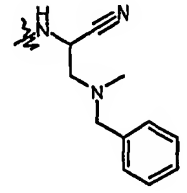
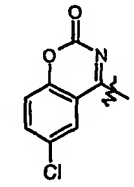
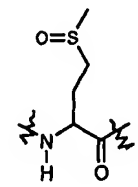
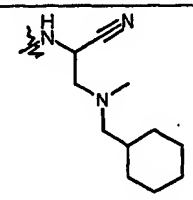
A36		B35		C36	
A37		B37		C37	
A38		B38		C38	
A39		B39		C39	
A40		B40		C40	
A41		B41		C41	
A42		B42		C42	

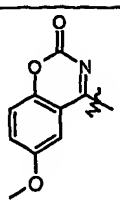
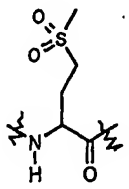
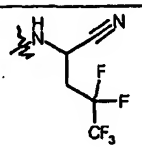
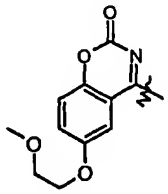
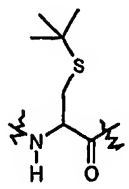
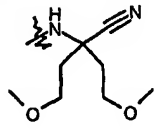
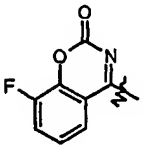
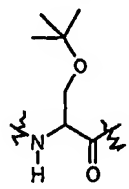
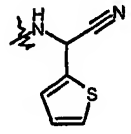
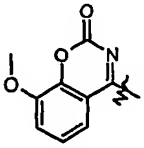
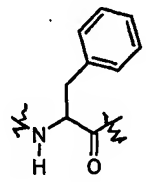
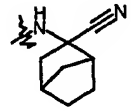
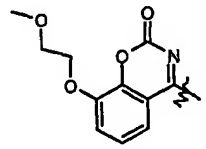
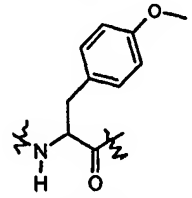
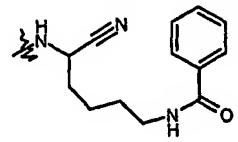
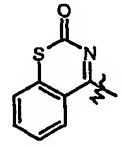
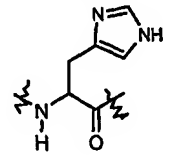
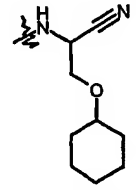
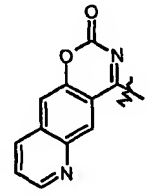
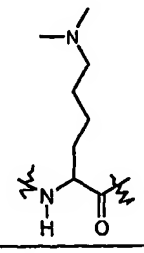
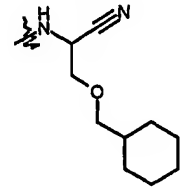
A43		B43		C43	
A44		B44		C44	
A45		B45		C45	
A46		B46		C46	
A47		B47		C47	
A48		B48		C48	
A49		B49		C49	

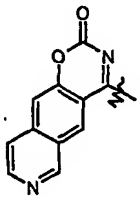
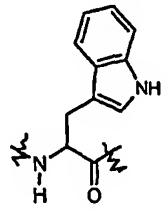
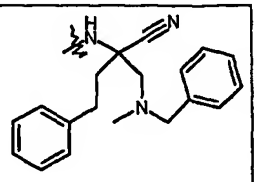
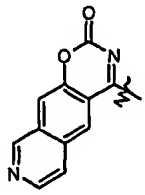
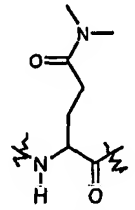
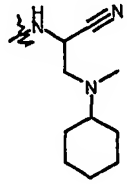
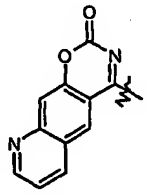
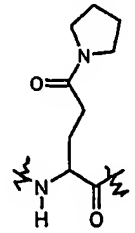
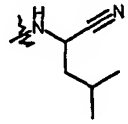
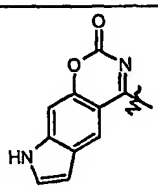
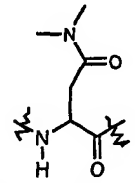
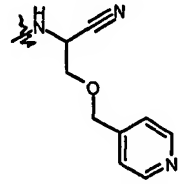
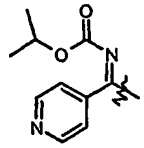
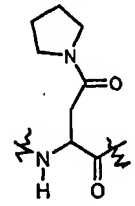
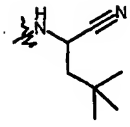
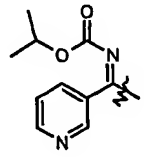
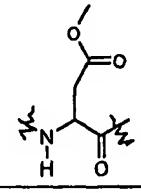
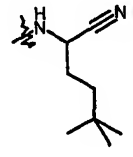
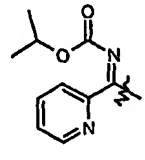
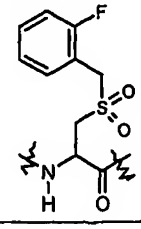
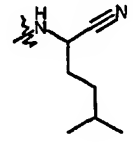
A50		B50		C50	
A51		B51		C51	
A52		B52		C52	
A53		B53		C53	
A54		B54		C54	
A55		B55		C55	
A56		B56		C56	

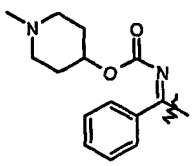
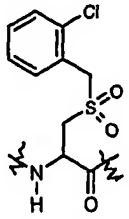
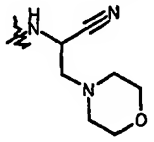
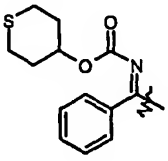
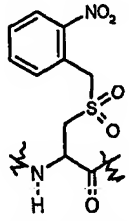
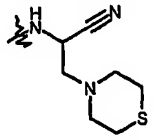
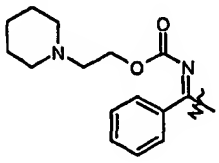
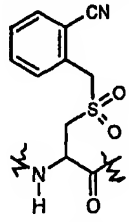
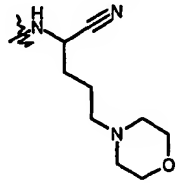
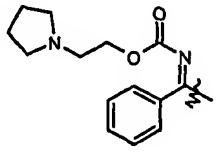
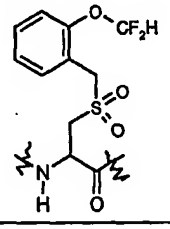
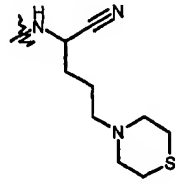
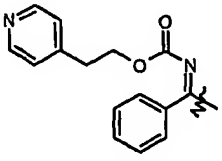
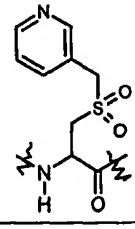
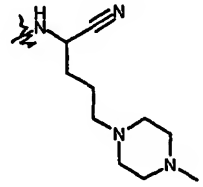
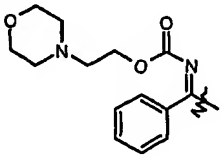
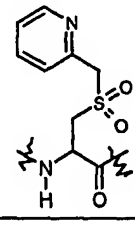
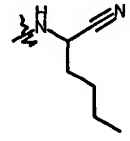
A57		B57		C57	
A58		B58		C58	
A59		B59		C59	
A60		B60		C60	
A61		B61		C61	
A62		B62		C62	
A63		B63		C63	

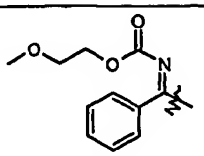
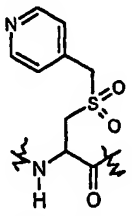
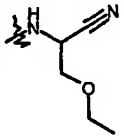
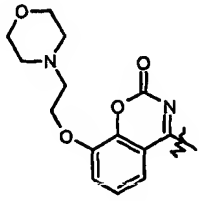
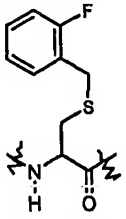
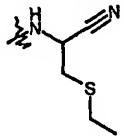
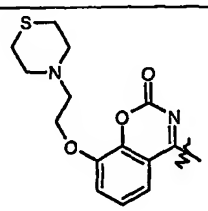
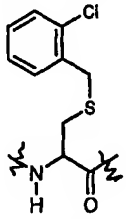
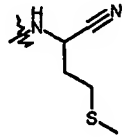
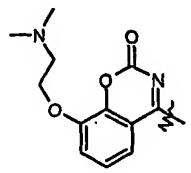
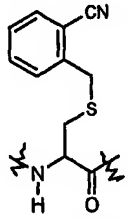
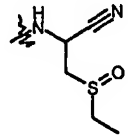
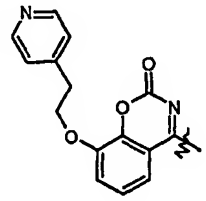
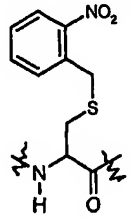
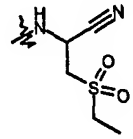
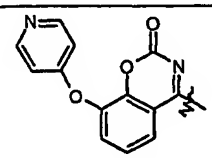
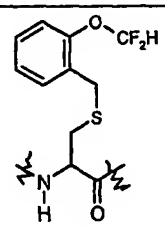
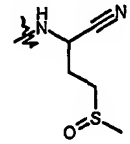
A64		B64		C64	
A65		B65		C65	
A66		B66		C66	
A67		B67		C67	
A68		B68		C68	
A69		B69		C69	
A70		B70		C70	

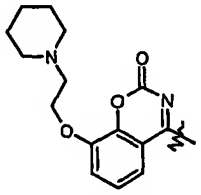
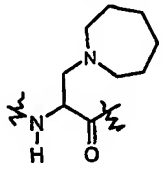
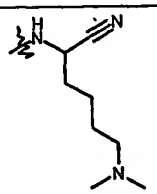
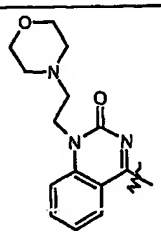
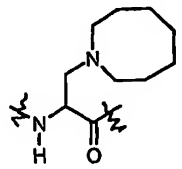
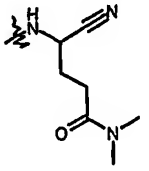
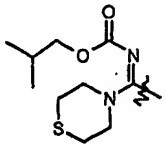
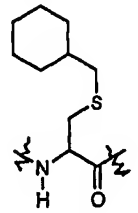
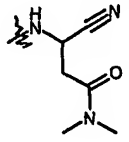
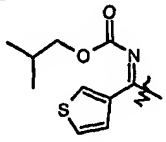
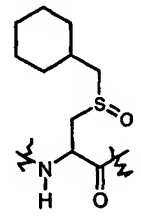
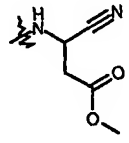
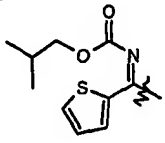
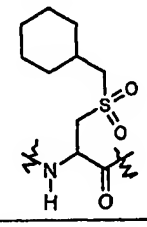
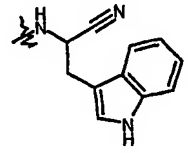
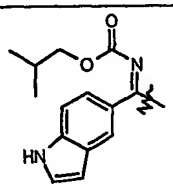
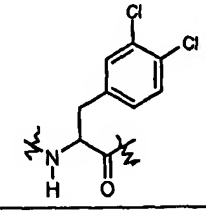
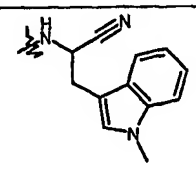
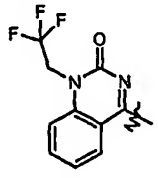
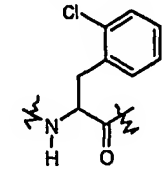
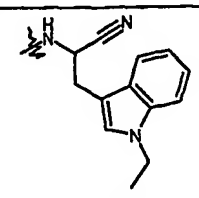
A71		B71		C71	
A72		B72		C72	
A73		B73		C73	
A74		B74		C74	
A75		B75		C75	
A76		B76		C76	

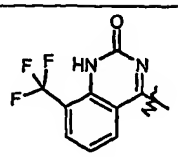
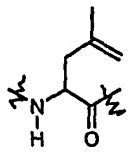
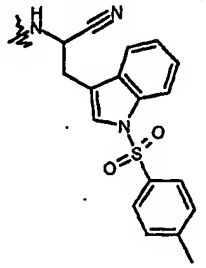
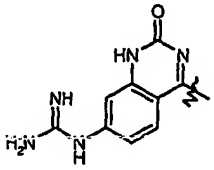
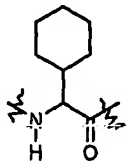
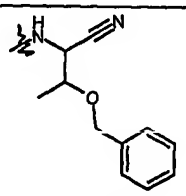
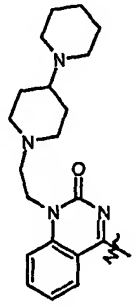
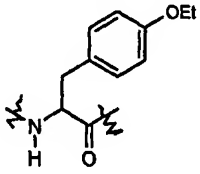
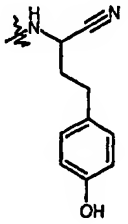
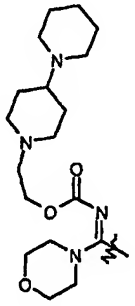
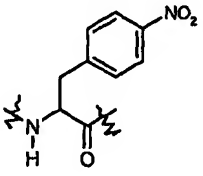
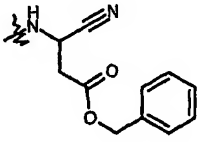
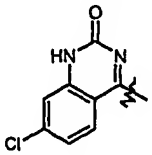
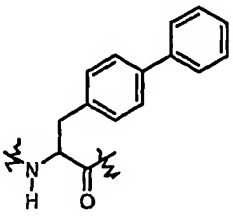
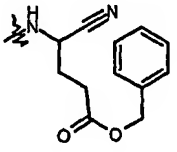
A77		B77		C77	
A78		B78		C78	
A79		B79		C79	
A80		B80		C80	
A81		B81		C81	
A82		B82		C82	
A83		B83		C83	

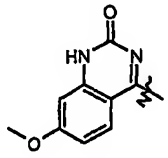
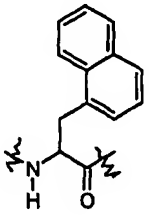
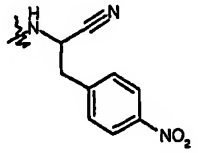
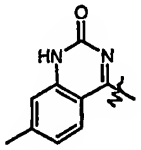
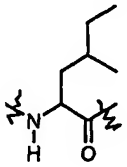
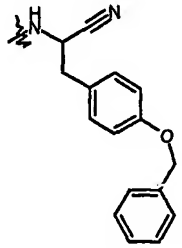
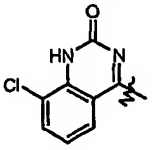
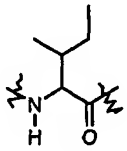
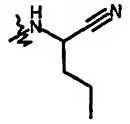
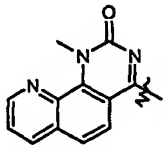
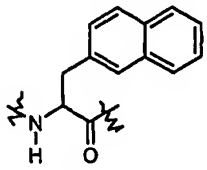
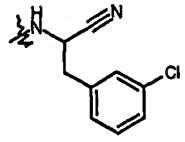
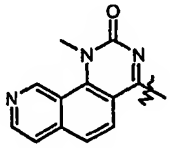
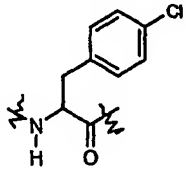
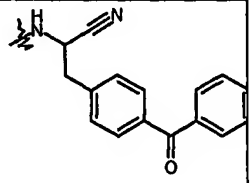
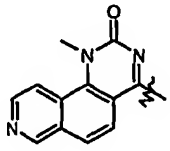
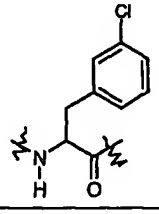
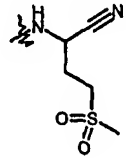
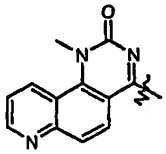
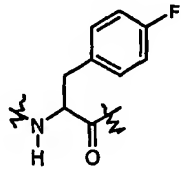
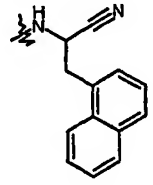
A84		B84		C84	
A85		B85		C85	
A86		B86		C86	
A87		B87		C87	
A88		B88		C88	
A89		B89		C89	
A90		B90		C90	

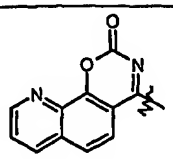
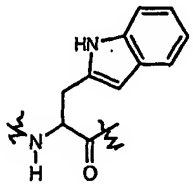
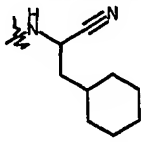
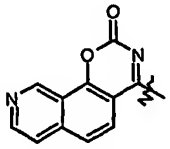
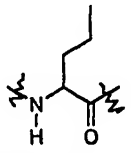
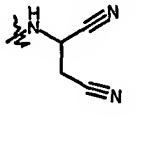
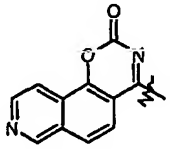
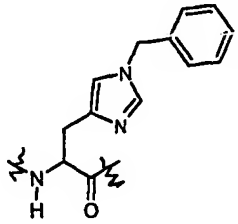
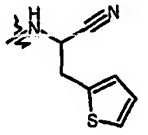
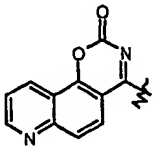
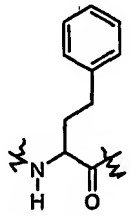
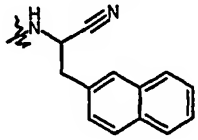
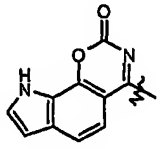
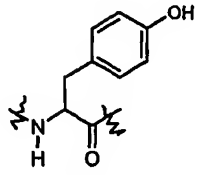
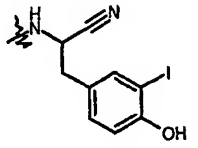
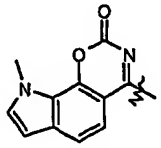
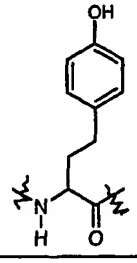
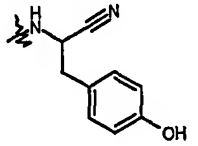
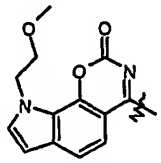
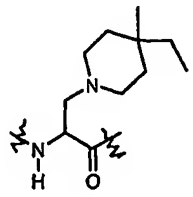
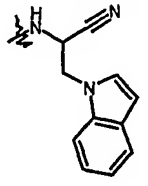
A91		B91		C91	
A92		B92		C92	
A93		B93		C93	
A94		B94		C94	
A95		B95		C95	
A96		B96		C96	

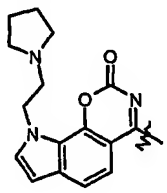
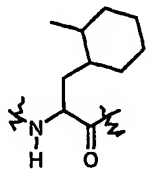
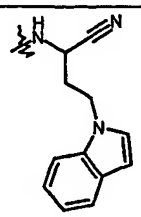
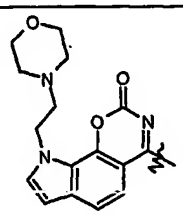
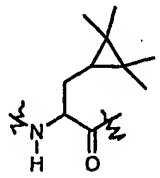
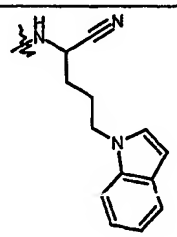
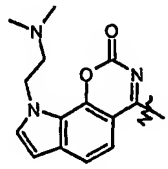
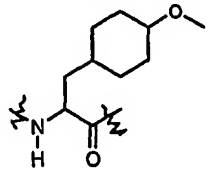
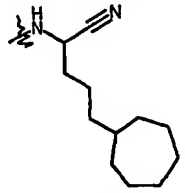
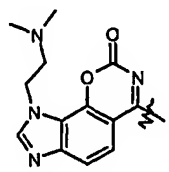
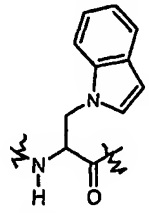
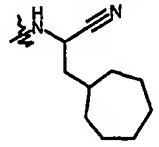
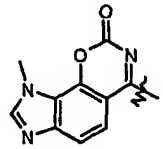
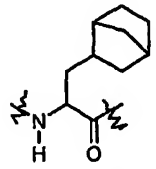
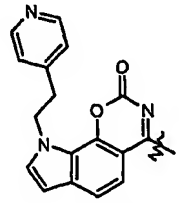
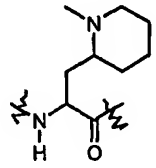
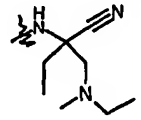
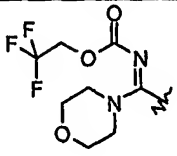
A97		B97		C97	
A98		B98		C98	
A99		B99		C99	
A100		B100		C100	
A101		B101		C101	
A102		B102		C102	

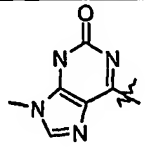
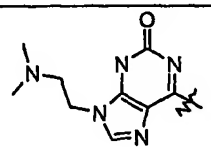
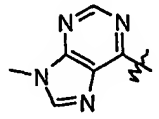
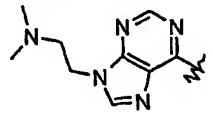
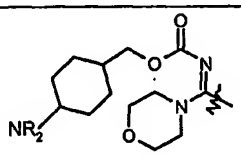
A103		B103		C103	
A104		B104		C104	
A105		B105		C105	
A106		B106		C106	
A107		B107		C107	
A108		B108		C108	
A109		B109		C109	

A110		B110		C110	
A111		B111		C111	
A112		B112		C112	
A113		B113		C113	
A114		B114		C114	

A115		B115		C115	
A116		B116		C116	
A117		B117		C117	
A118		B118		C118	
A119		B119		C119	
A120		B120		C120	
A121		B121		C121	

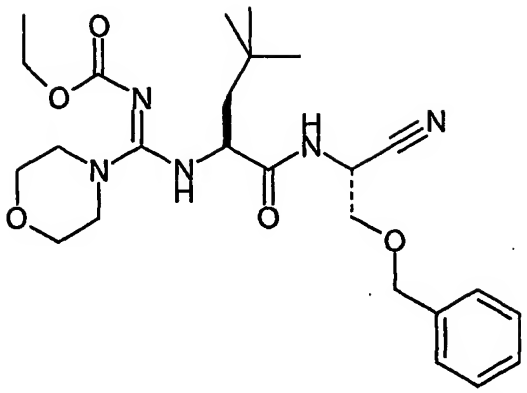
A122		B122		C122	
A123		B123		C123	
A124		B124		C124	
A125		B125		C125	
A126		B126		C126	
A127		B127		C127	
A128		B128		C128	

A129		B129		C129	
A130		B130		C130	
A131		B131		C131	
A132		B132		C132	
A133		B133		C133	
A134		B134		C134	
A135					

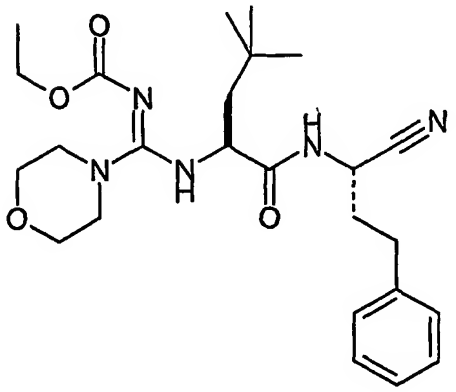
A136					
A137					
A138					
A139					
A140	 R is hydrogen or alkyl				

and the pharmaceutically acceptable derivatives thereof.

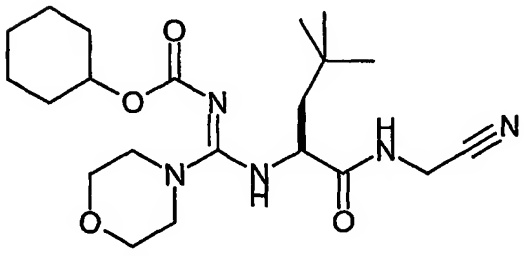
The following compounds can be synthesized by the General schemes, methods described in the experimental section of this document and analogous methods known to those skilled in the art without undue experimentation. Preferred compounds will possess desirable inhibition activity of Cathepsin S in a cell based assay as described in Riese, R.J. et al., Immunity, 1996, 4, 357-366, incorporated herein by reference.



({1-[(Benzyloxymethyl-cyano-methyl)-carbamoyl]-3,3-dimethyl-butylimino}-morpholin-4-yl-methyl)-carbamic acid ethyl ester



{[1-(1-Cyano-3-phenyl-propylcarbamoyl)-3,3-dimethyl-butylimino]-morpholin-4-yl-methyl}-carbamic acid ethyl ester



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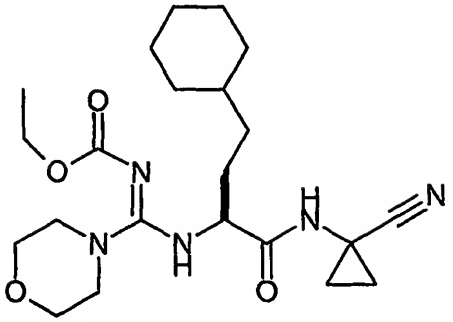

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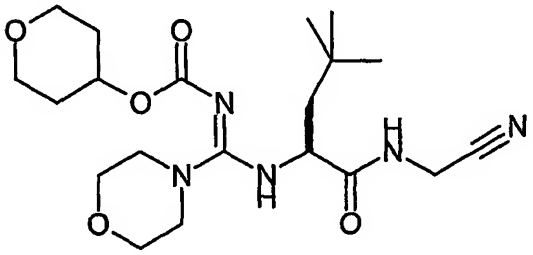

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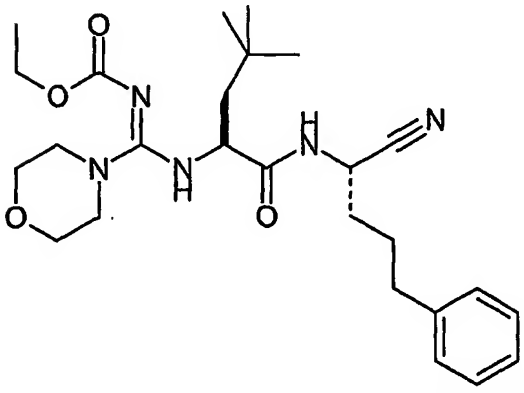

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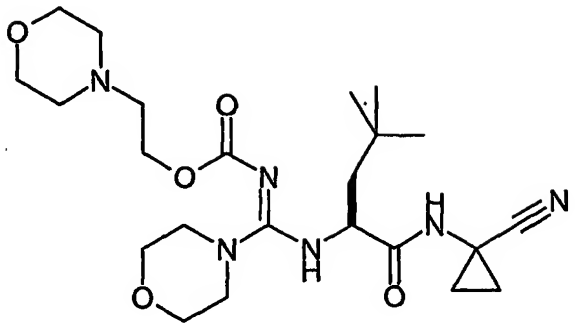

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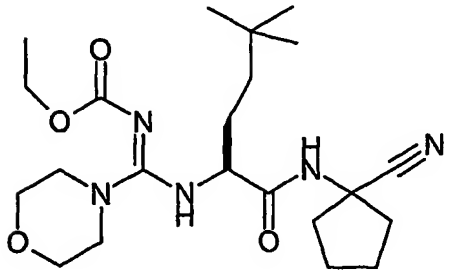

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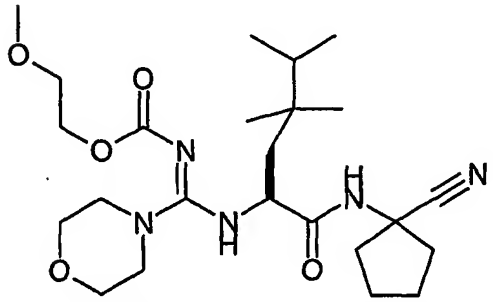

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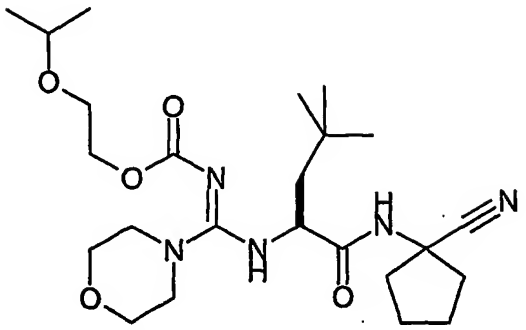
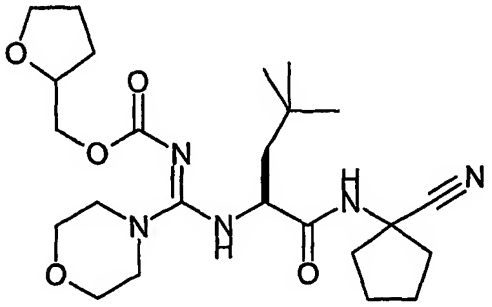


{[1-(1-Cyano-cyclopentylcarbamoyl)-3,3-dimethyl-butylimino]-morpholin-4-yl-methyl}-carbamic acid 2-isopropoxy-ethyl ester



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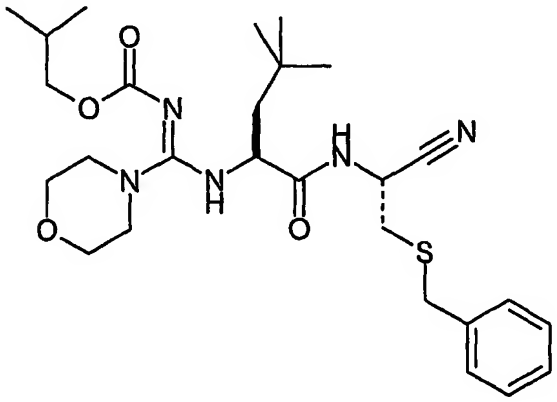
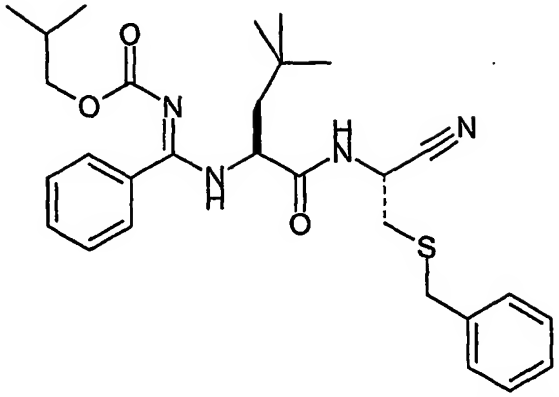


({1-[(Benzylsulfanylmethyl-cyano-methyl)-carbamoyl]-3,3-dimethyl-butylimino}-morpholin-4-yl-methyl)-carbamic acid isobutyl ester



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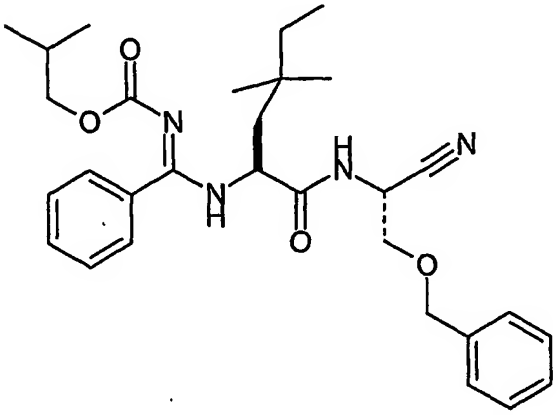

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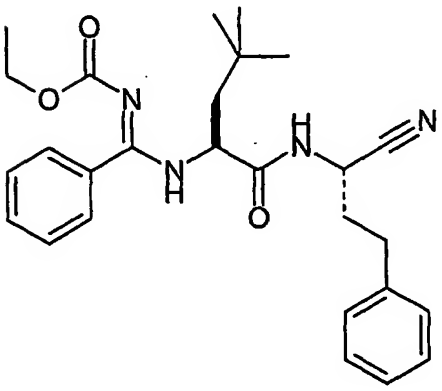

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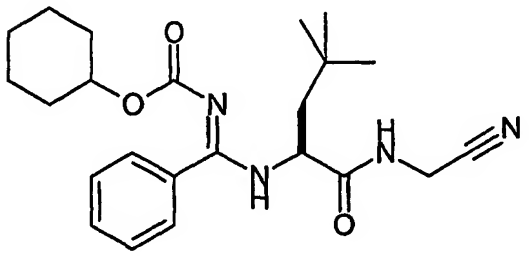

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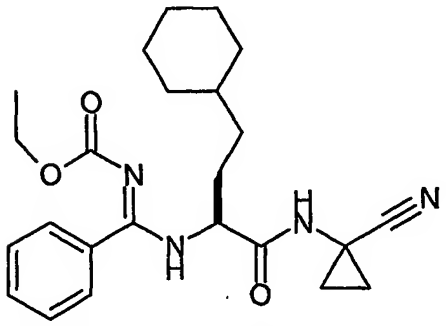

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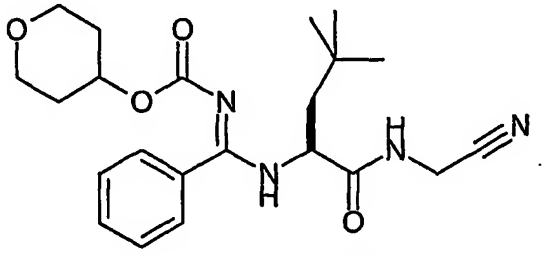
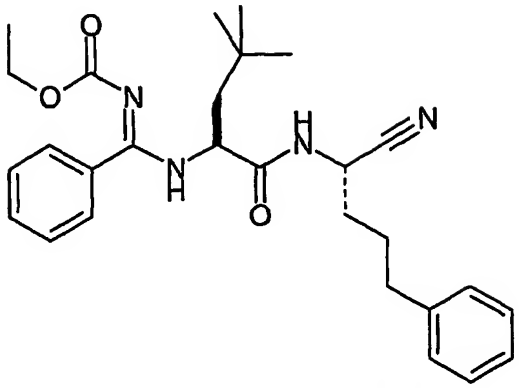


{[1-(Cyanomethyl-carbamoyl)-3,3-dimethyl-butylimino]-phenyl-methyl}-carbamic acid tetrahydro-pyran-4-yl ester



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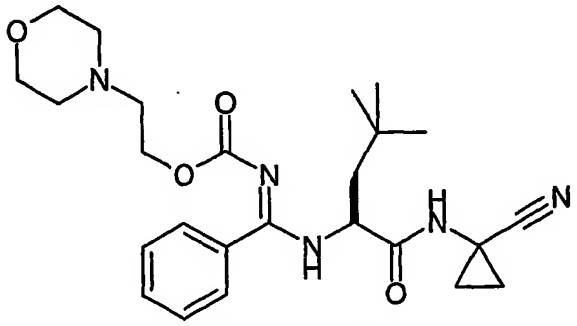

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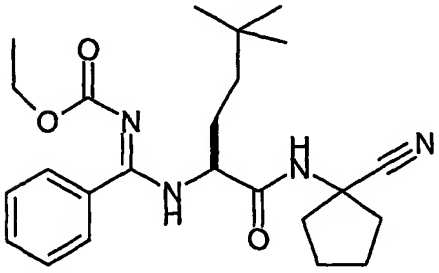

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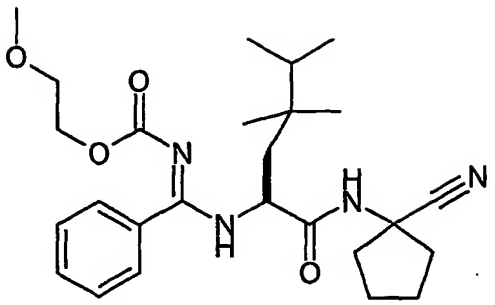

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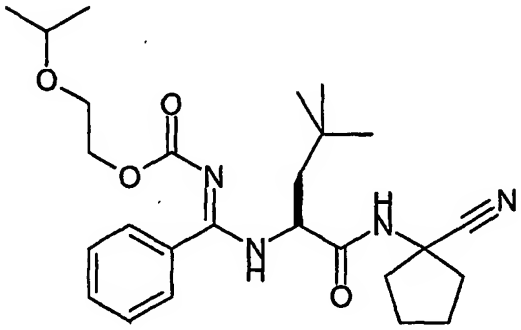

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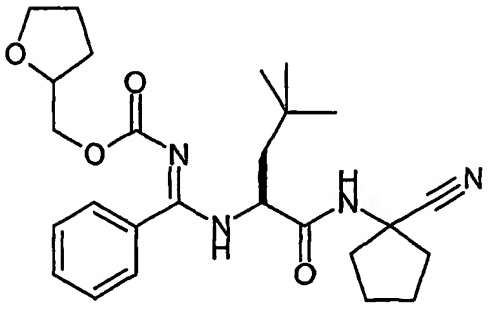

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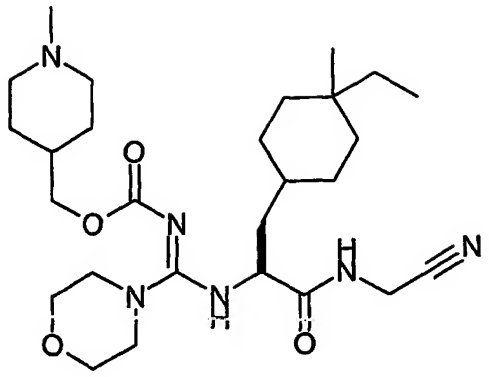
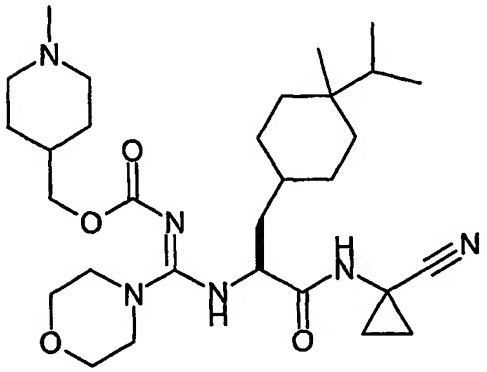
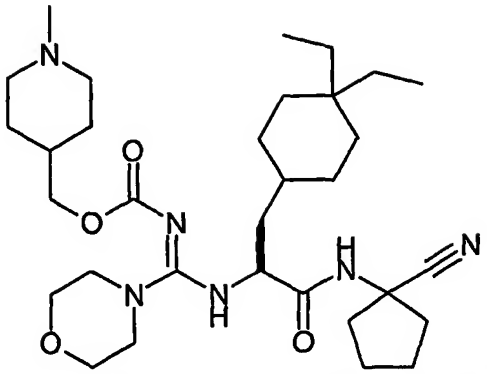


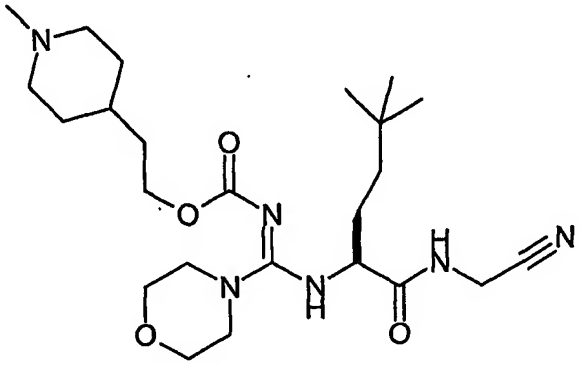
{[1-(Cyanomethyl-carbamoyl)-2-(4-ethyl-4-methyl-cyclohexyl)-ethylimino]-morpholin-4-yl-methyl}-carbamic acid 1-methyl-piperidin-4-ylmethyl ester



{[1-(1-Cyano-cyclopropylcarbamoyl)-2-(4-isopropyl-4-methyl-cyclohexyl)-ethylimino]-morpholin-4-yl-methyl}-carbamic acid 1-methyl-piperidin-4-ylmethyl ester



{[1-(1-Cyano-cyclopentylcarbamoyl)-2-(4,4-diethyl-cyclohexyl)-ethylimino]-morpholin-4-yl-methyl}-carbamic acid 1-methyl-piperidin-4-ylmethyl ester



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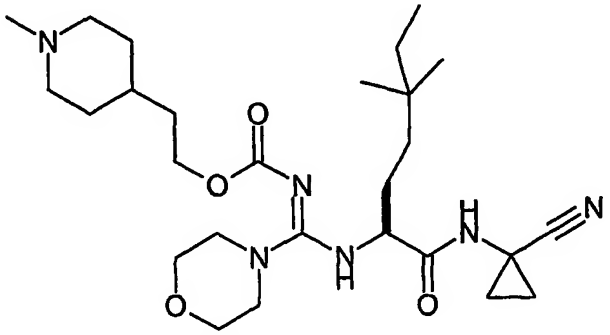

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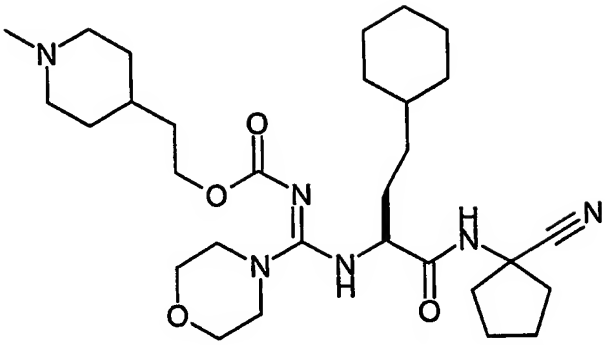

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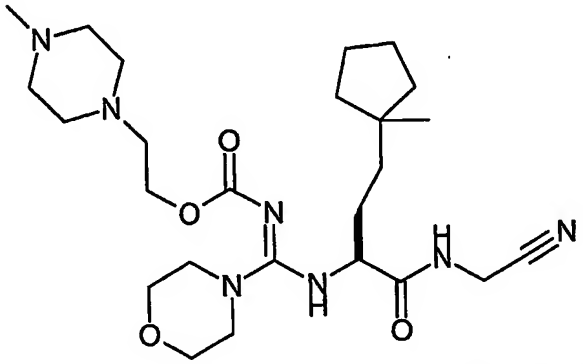

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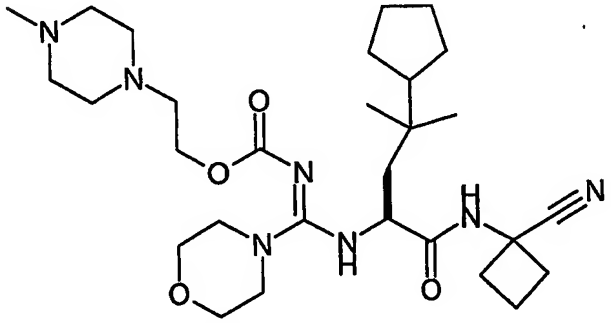

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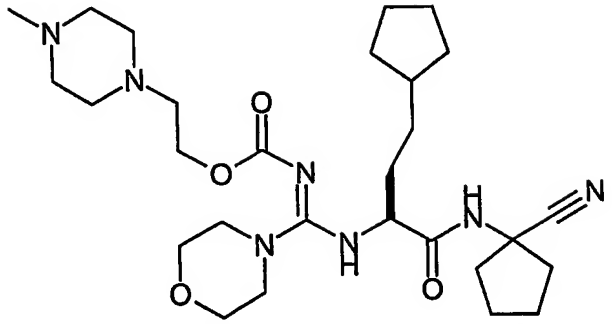

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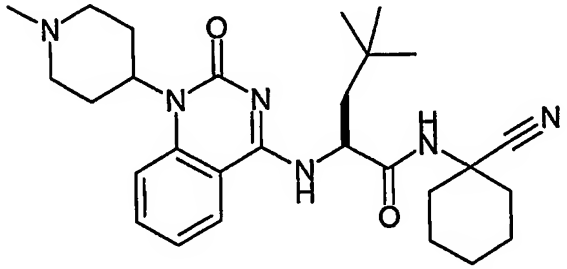
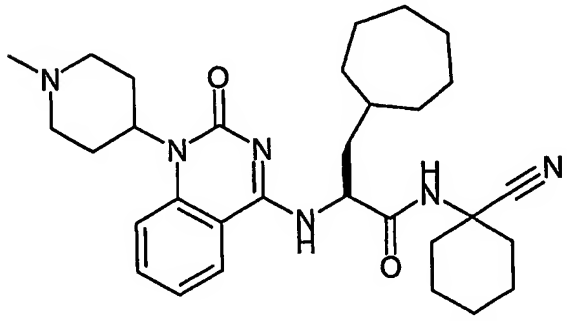
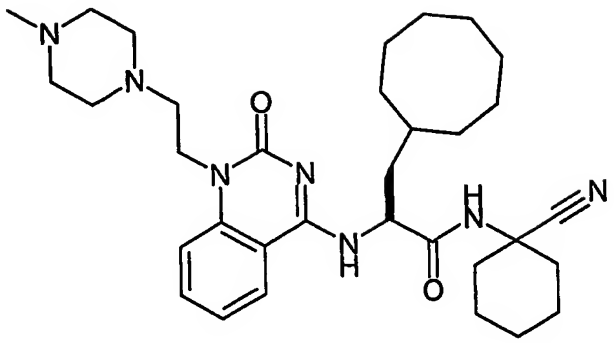


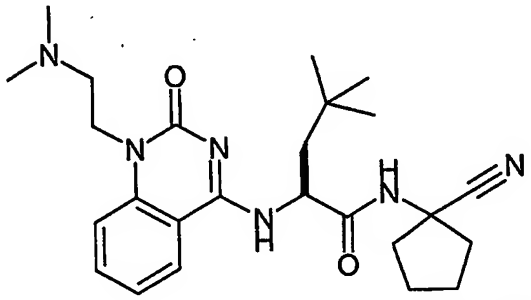
4,4-Dimethyl-2-[1-(1-methyl-piperidin-4-yl)-2-oxo-2,3-dihydro-1*H*-quinazolin-4-ylideneamino]-pentanoic acid (1-cyano-cyclohexyl)-amide



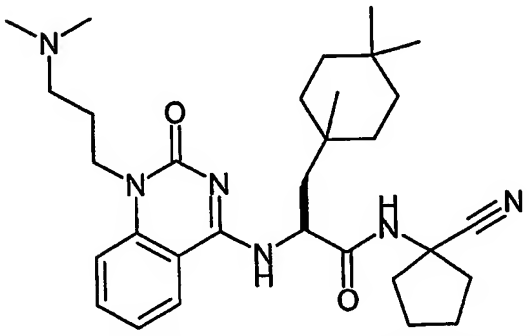
N-(1-Cyano-cyclohexyl)-3-cycloheptyl-2-[1-(1-methyl-piperidin-4-yl)-2-oxo-2,3-dihydro-1*H*-quinazolin-4-ylideneamino]-propionamide



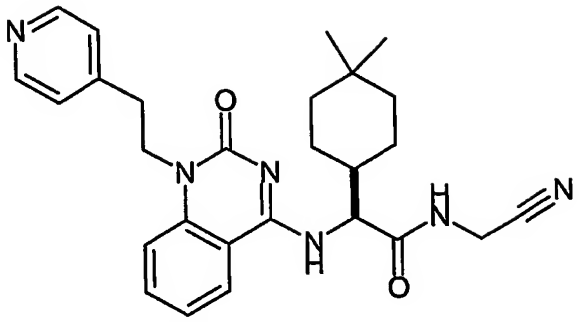
N-(1-Cyano-cyclohexyl)-3-cyclooctyl-2-{1-[2-(4-methyl-piperazin-1-yl)-ethyl]-2-oxo-2,3-dihydro-1*H*-quinazolin-4-ylideneamino}-propionamide



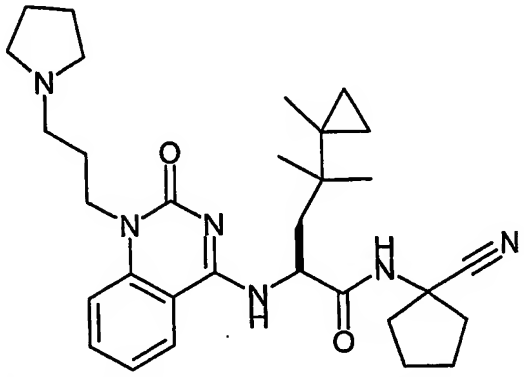
2-[1-(2-Dimethylamino-ethyl)-2-oxo-2,3-dihydro-1*H*-quinazolin-4-ylideneamino]-4,4-dimethyl-pentanoic acid (1-cyano-cyclopentyl)-amide



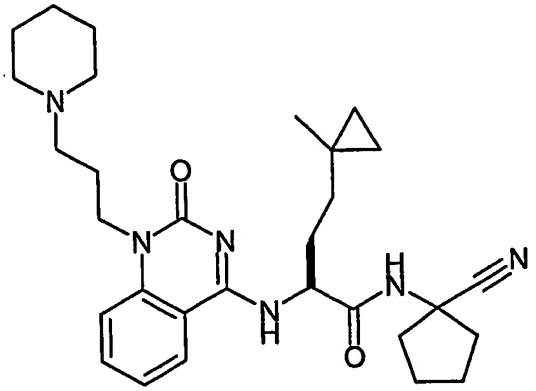
N-(1-Cyano-cyclopentyl)-2-[1-(3-dimethylamino-propyl)-2-oxo-2,3-dihydro-1*H*-quinazolin-4-ylideneamino]-3-(1,4,4-trimethyl-cyclohexyl)-propionamide



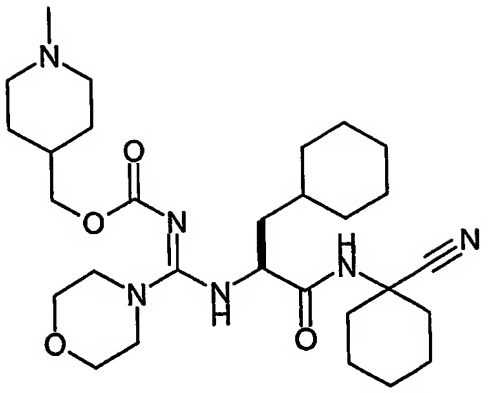
N-Cyanomethyl-2-(4,4-dimethyl-cyclohexyl)-2-[2-oxo-1-(2-pyridin-4-yl-ethyl)-2,3-dihydro-1*H*-quinazolin-4-ylideneamino]-acetamide



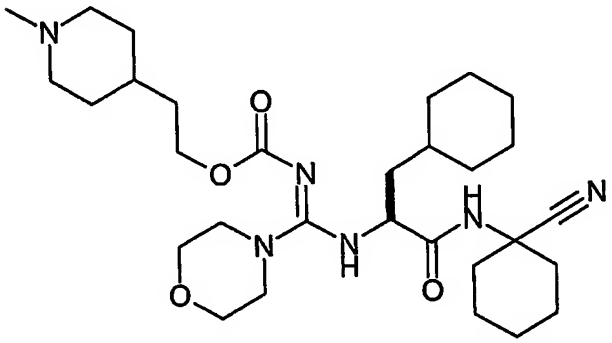
4-Methyl-4-(1-methyl-cyclopropyl)-2-[2-oxo-1-(3-pyrrolidin-1-yl-propyl)-2,3-dihydro-1*H*-quinazolin-4-ylideneamino]-pentanoic acid (1-cyano-cyclopentyl)-amide



N-(1-Cyano-cyclopentyl)-4-(1-methyl-cyclopropyl)-2-[2-oxo-1-(3-piperidin-1-yl-propyl)-2,3-dihydro-1*H*-quinazolin-4-ylideneamino]-butyramide



{[1-(1-Cyano-cyclohexylcarbamoyl)-2-cyclohexyl-ethylimino]-morpholin-4-yl-methyl}-carbamic acid 1-methyl-piperidin-4-ylmethyl ester



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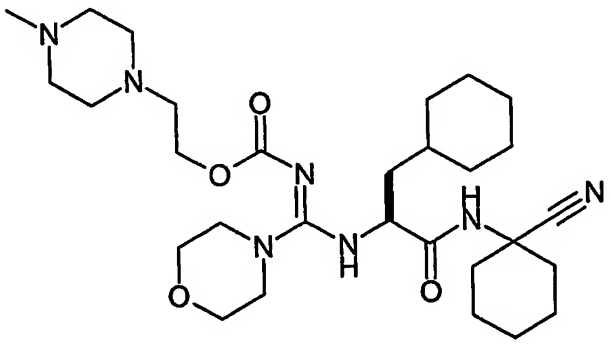

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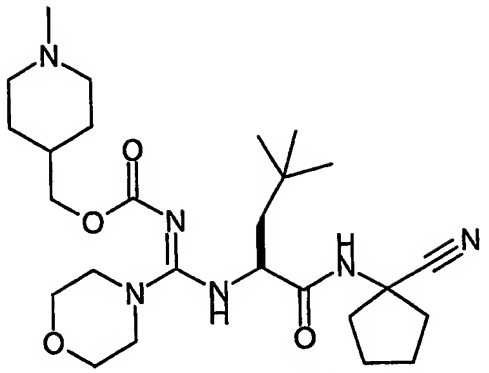

{[1-(1-Cyano-cyclopentylcarbamoyl)-3,3-dimethyl-butylimino]-morpholin-4-yl-methyl}-carbamic acid 1-methyl-piperidin-4-ylmethyl ester

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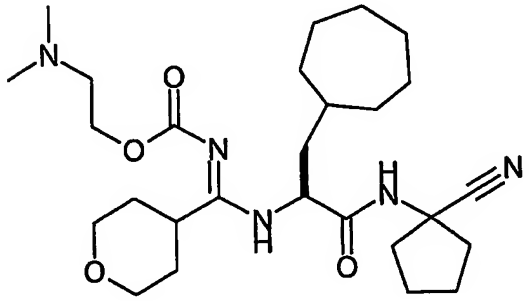
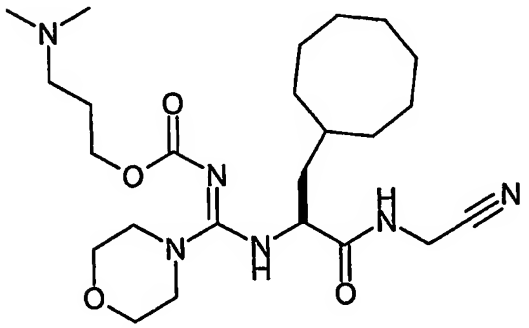


[[1-(1-Cyano-cyclopentylcarbamoyl)-2-cycloheptyl-ethylimino]-(tetrahydro-pyran-4-yl)-methyl]-carbamic acid 2-dimethylamino-ethyl ester

10



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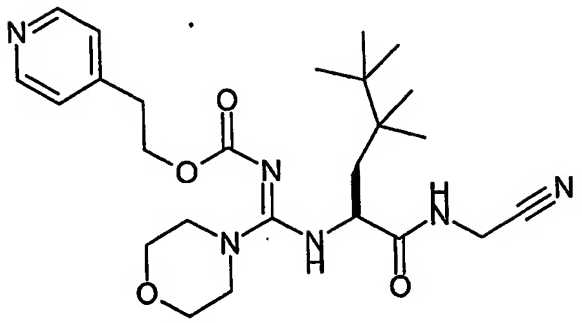

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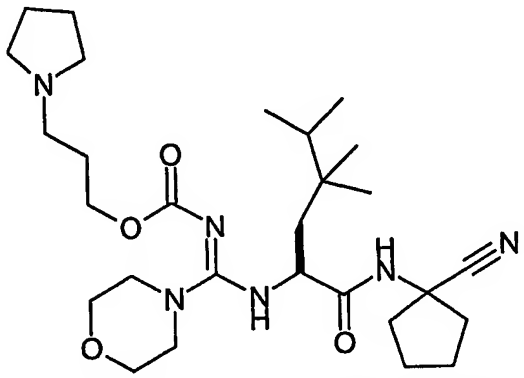

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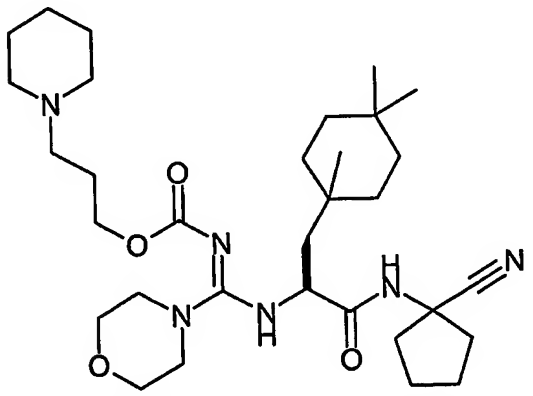
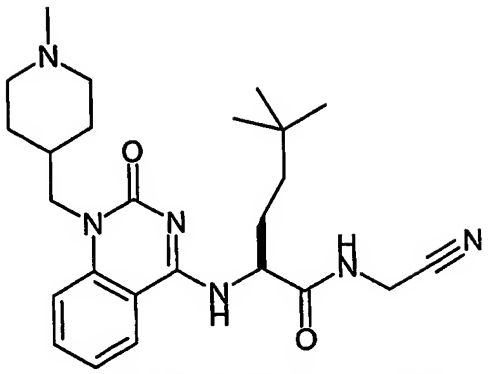
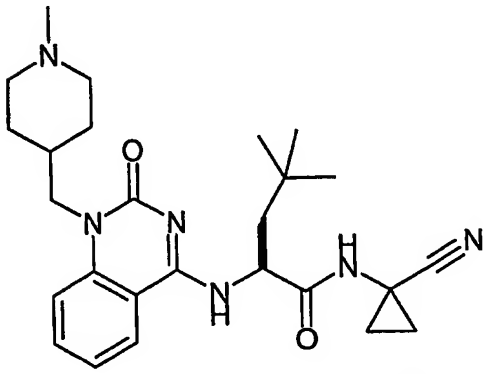


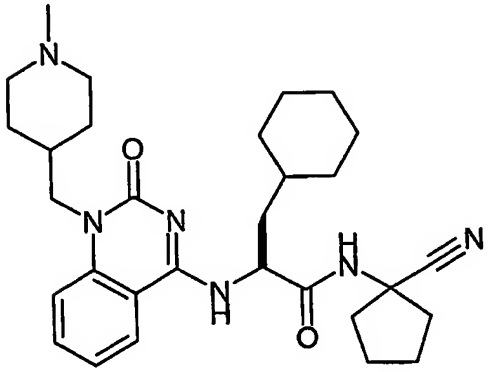
{[1-(1-Cyano-cyclopentylcarbamoyl)-2-(1,4,4-trimethyl-cyclohexyl)-ethylimino]-morpholin-4-yl-methyl}-carbamic acid 3-piperidin-1-yl-propyl ester



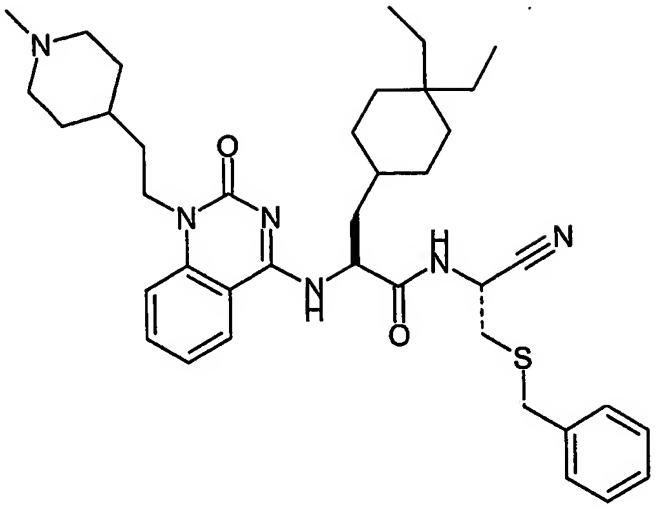
5,5-Dimethyl-2-[1-(1-methyl-piperidin-4-ylmethyl)-2-oxo-2,3-dihydro-1*H*-quinazolin-4-ylideneamino]-hexanoic acid cyanomethyl-amide



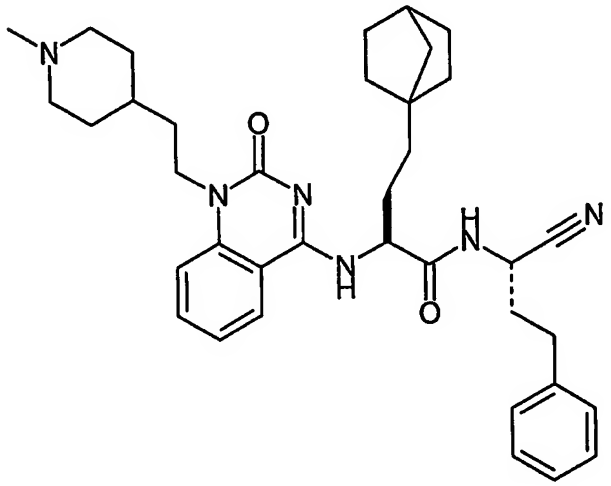
4,4-Dimethyl-2-[1-(1-methyl-piperidin-4-ylmethyl)-2-oxo-2,3-dihydro-1*H*-quinazolin-4-ylideneamino]-pentanoic acid (1-cyano-cyclopropyl)-amide



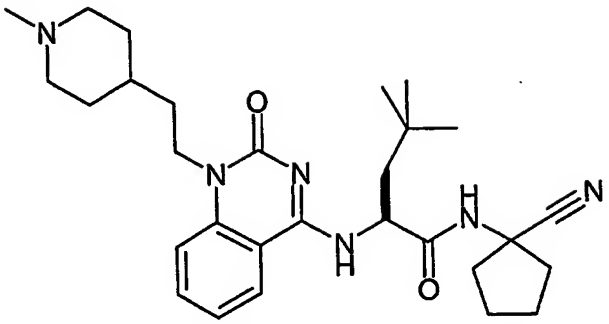
N-(1-Cyano-cyclopentyl)-3-cyclohexyl-2-[1-(1-methyl-piperidin-4-ylmethyl)-2-oxo-2,3-dihydro-1*H*-quinazolin-4-ylideneamino]-propionamide



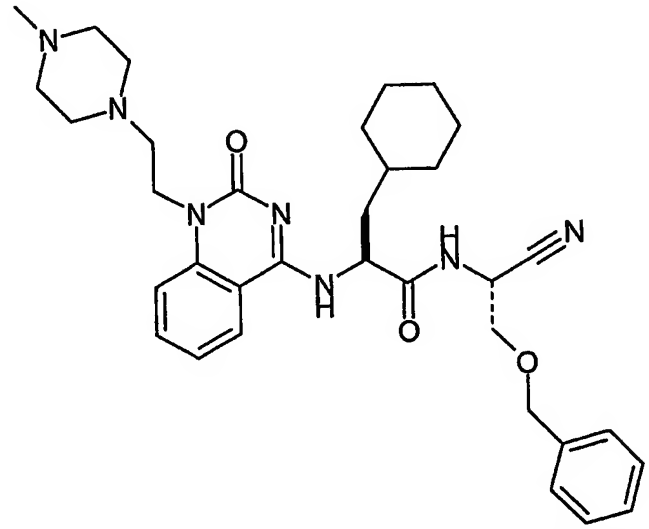
N-(Benzylsulfanylmethyl-cyano-methyl)-3-(4,4-diethyl-cyclohexyl)-2-{1-[2-(1-methyl-piperidin-4-yl)-ethyl]-2-oxo-2,3-dihydro-1*H*-quinazolin-4-ylideneamino}-propionamide



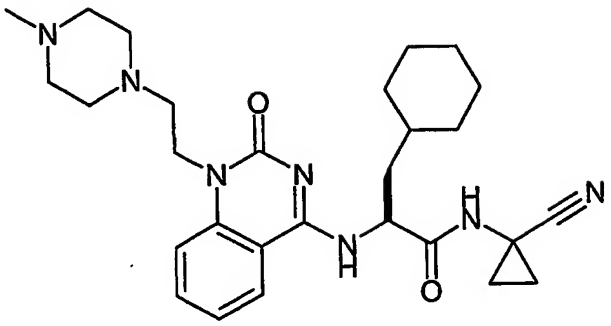
4-Bicyclo[2.2.1]hept-1-yl-*N*-(1-cyano-3-phenyl-propyl)-2-{1-[2-(1-methyl-piperidin-4-yl)-ethyl]-2-oxo-2,3-dihydro-1*H*-quinazolin-4-ylideneamino}-butyramide



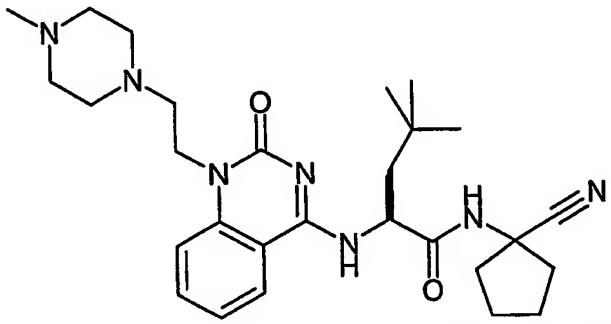
4,4-Dimethyl-2-{1-[2-(1-methyl-piperidin-4-yl)-ethyl]-2-oxo-2,3-dihydro-1*H*-quinazolin-4-ylideneamino}-pentanoic acid (1-cyano-cyclopentyl)-amide



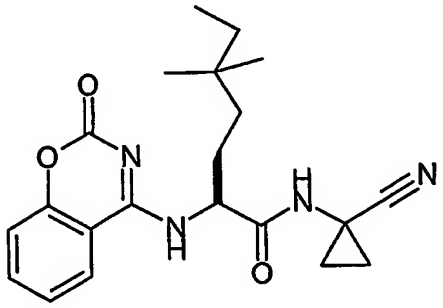
N-(Benzyloxymethyl-cyano-methyl)-3-cyclohexyl-2-{1-[2-(4-methyl-piperazin-1-yl)-ethyl]-2-oxo-2,3-dihydro-1*H*-quinazolin-4-ylideneamino}-propionamide



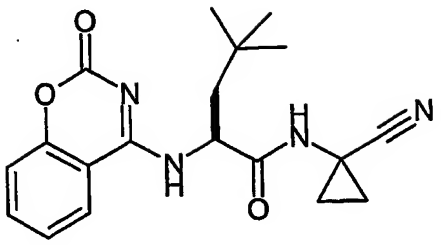
N-(1-Cyano-cyclopropyl)-3-cyclohexyl-2-{1-[2-(4-methyl-piperazin-1-yl)-ethyl]-2-oxo-2,3-dihydro-1*H*-quinazolin-4-ylideneamino}-propionamide



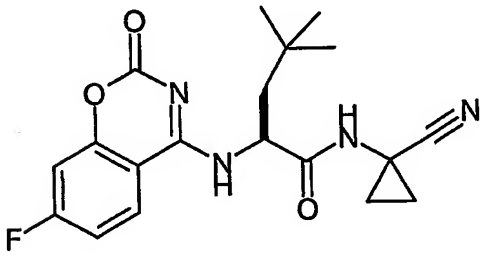
4,4-Dimethyl-2-{1-[2-(4-methyl-piperazin-1-yl)-ethyl]-2-oxo-2,3-dihydro-1*H*-quinazolin-4-ylideneamino}-pentanoic acid (1-cyano-cyclopentyl)-amide



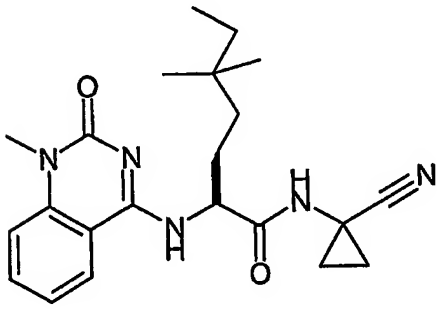
(S)-5,5-Dimethyl-2-(2-oxo-2*H*-benzo[*e*][1,3]oxazin-4-ylamino)-heptanoic acid (1-cyano-cyclopropyl)-amide



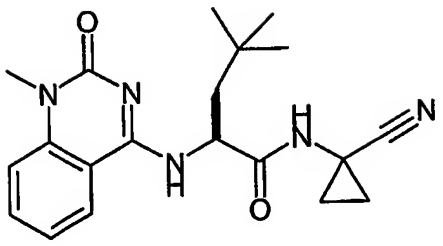
(S)-4,4-Dimethyl-2-(2-oxo-2*H*-benzo[*e*][1,3]oxazin-4-ylamino)-pentanoic acid (1-cyano-cyclopropyl)-amide



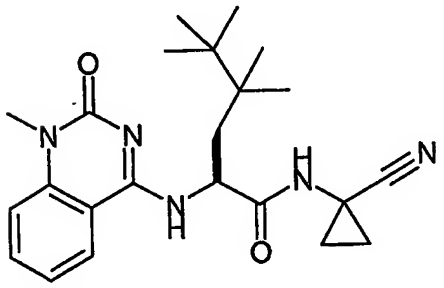
(S)-2-(7-Fluoro-2-oxo-2*H*-benzo[*e*][1,3]oxazin-4-ylamino)-4,4-dimethyl-pentanoic acid (1-cyano-cyclopropyl)-amide



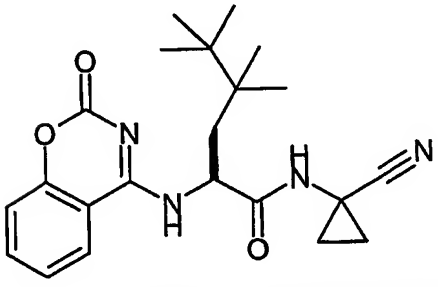
(S)-5,5-Dimethyl-2-(1-methyl-2-oxo-1,2-dihydro-quinazolin-4-ylamino)-heptanoic acid (1-cyano-cyclopropyl)-amide



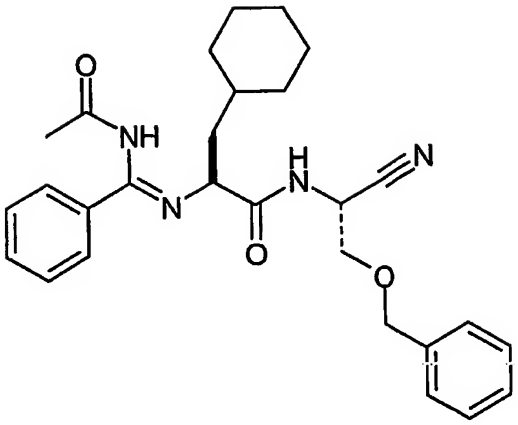
(S)-4,4-Dimethyl-2-(1-methyl-2-oxo-1,2-dihydro-quinazolin-4-ylamino)-pentanoic acid (1-cyano-cyclopropyl)-amide



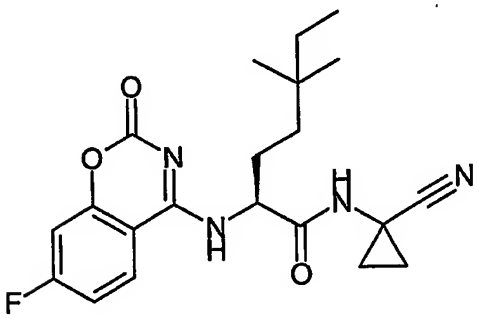
(S)-4,4,5,5-Tetramethyl-2-(1-methyl-2-oxo-1,2-dihydro-quinazolin-4-ylamino)-hexanoic acid (1-cyano-cyclopropyl)-amide



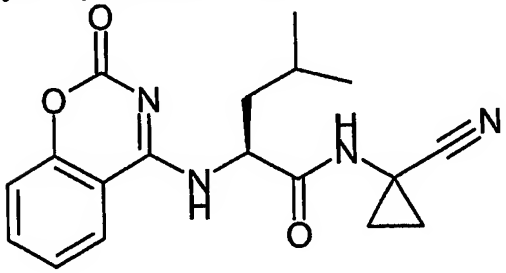
(S)-4,4,5,5-Tetramethyl-2-(2-oxo-2*H*-benzo[*e*][1,3]oxazin-4-ylamino)-hexanoic acid (1-cyano-cyclopropyl)-amide



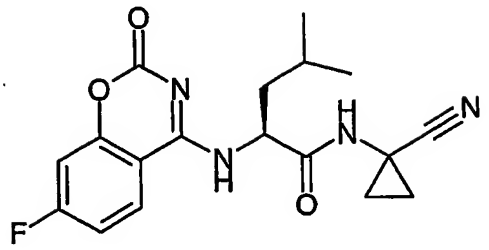
2-[(Acetylimino-phenyl-methyl)-amino]-N(benzyloxymethyl-cyano-methyl)-3-cyclohexyl-propionamide.



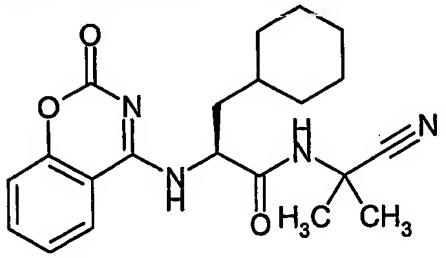
2-(7-Fluoro-2-oxo-*2H*-benxo[*e*][1,3]oxazin-4-ylamino)-5,5-dimethyl-heptanoic acid (1-cyano-cyclopropyl)-amide



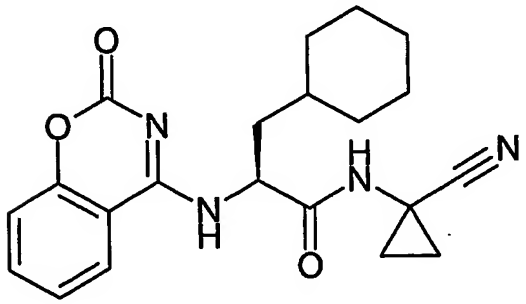
4-Methyl-2-(2-oxo-*2H*-benzo[*e*][1,3]oxazin-4-ylamino)-pentanoic acid (1-cyano-cyclopropyl)-amide



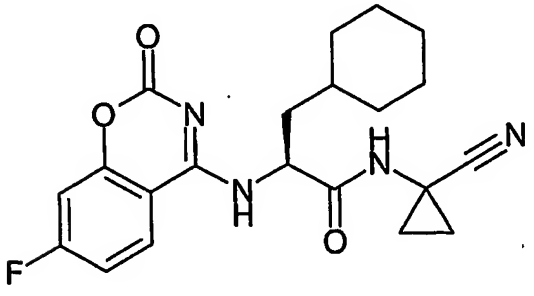
2-(7-Fluoro-2-oxo-*2H*-benzo[*e*][1,3]oxazin-4-ylamino)-4-methyl-pentanoic acid (1-cyano-cyclopropyl)-amide



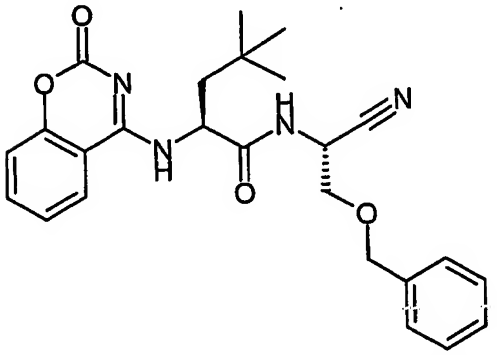
N-(Cyano-dimethyl-methyl)-3-cyclohexyl-2-(2-oxo-*2H*-benzo[*e*][1,3]oxazin-4-ylamino)-propionamide



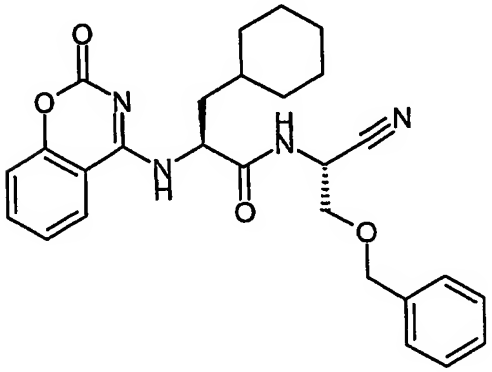
N-(1-Cyano-cyclopropyl)-3-cyclohexyl-2-(2-oxo-*2H*-benzo[*e*][1,3]oxazin-4-ylamino)-propionamide



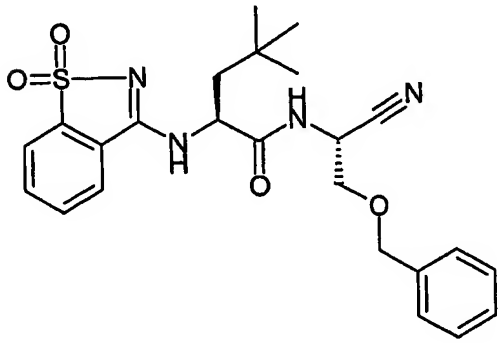
N-(1-Cyano-cyclopropyl)-3-cyclohexyl-2-(7-fluoro-2-oxo-*2H*-benzo[*e*][1,3]oxazin-4-ylamino)-propionamide



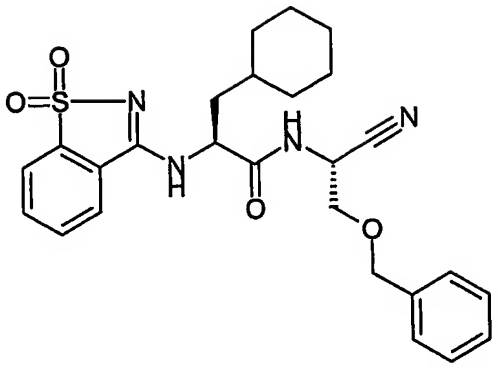
N-(Cyano-benzyloxymethyl -methyl)-3-cyclohexyl-2-(2-oxo-*2H*-benzo[*e*][1,3]oxazin-4-ylamino)-propionamide



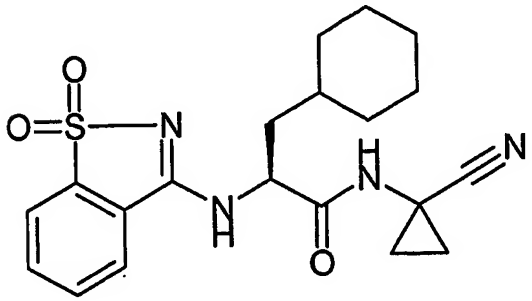
4,4-Dimethyl-2-(2-oxo-*2H*-benxo[*e*][1,3]oxazin-4-ylamino)-pentanoic acid (cyano-benzyloxymethyl-methyl)-amide



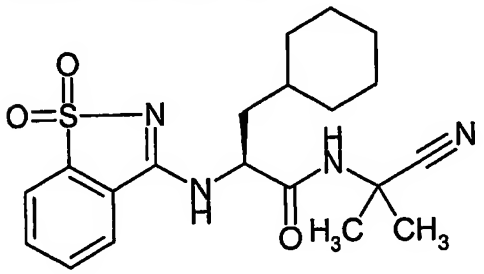
2-(1,1-Dioxo-*1H*-1λ^6-benzo[*d*]isothiazol-3-ylamino)-4,4-dimethyl-pentanoic acid (cyano-benzyloxymethyl-methyl)-amide



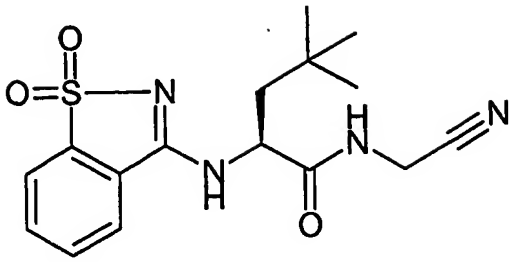
N-(Cyano-benzyloxymethyl-methyl)-3-cyclohexyl-2-(1,1-dioxo-*1H*-1λ^6-benzo[*d*]isothiazol-3-ylamino)-propionamide



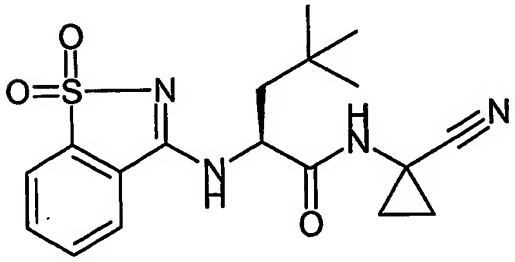
N-(1-Cyano-cylopropyl)-3-cyclohexyl-2-(1,1-dioxo-*1H*-1λ^6-benzo[*d*]isothiazol-3-ylamino)-propionamide



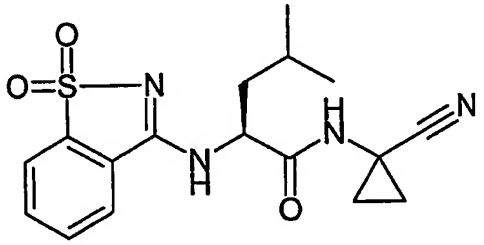
N-(Cyano-dimethyl-methyl)-3-cyclohexyl-2-(1,1-dioxo-*1H*-1λ^6-benzo[*d*]isothiazol-3-ylamino)-propionamide



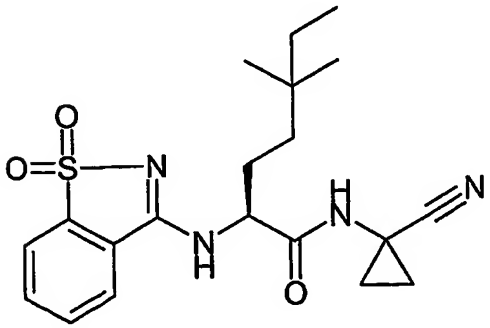
2-(1,1-Dioxo-*1H*-1λ^6-benzo[*d*]isothiazol-3-ylamino)-4,4-dimethyl-pentanoic acid cyanomethyl-amide



2-(1,1-Dioxo-*1H*-1λ^6-benzo[*d*]isothiazol-3-ylamino)-4,4-dimethyl-pentanoic acid (1-cyano-cyclopropyl)-amide



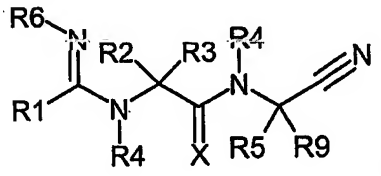
2-(1,1-Dioxo-*1H*-1λ^6-benzo[*d*]isothiazol-3-ylamino)-4-methyl-pentanoic acid (1-cyano-cyclopropyl)-amide



2-(1,1-Dioxo-*1H*-1λ^6-benzo[*d*]isothiazol-3-ylamino)-5,5-dimethyl-heptanoic acid (1-cyano-cyclopropyl)-amide

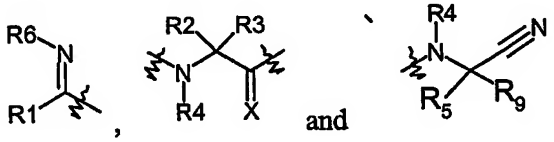
In another embodiment of the invention are compounds presented in Table II:

TABLE II



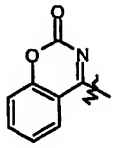
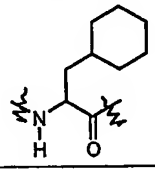
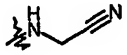
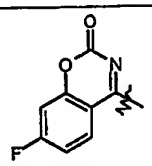
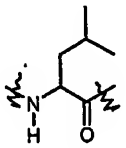
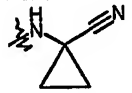
(Ia)

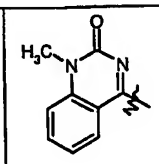
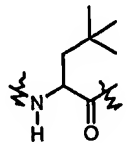
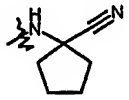
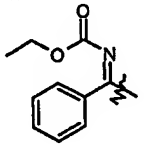
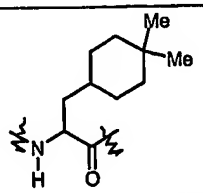
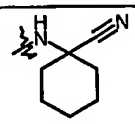
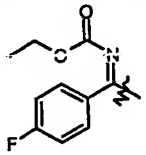
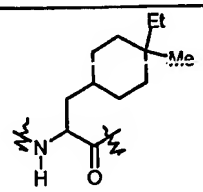
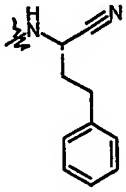
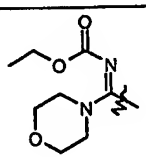
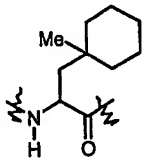
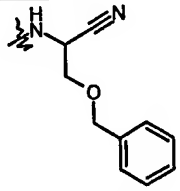
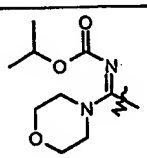
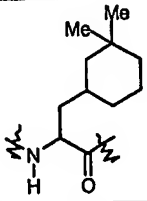
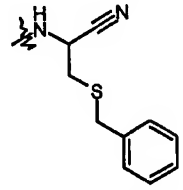
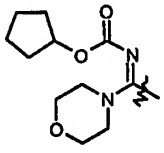
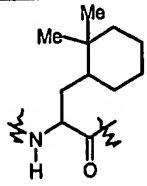
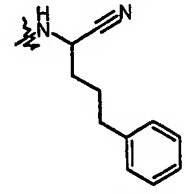
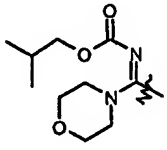
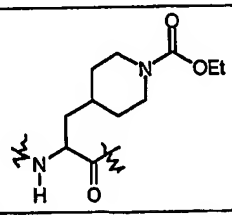
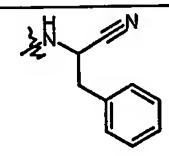
wherein for the Formula (Ia), the components

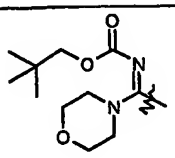
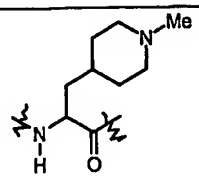
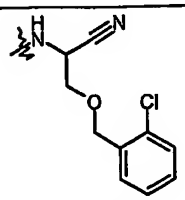
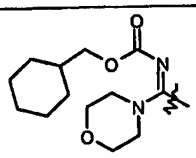
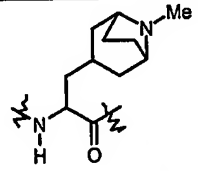
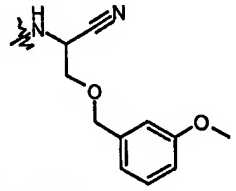
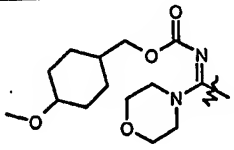
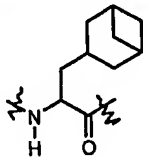
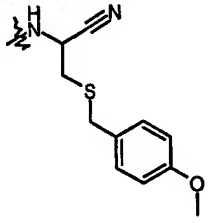
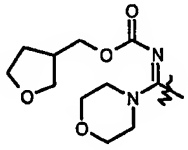
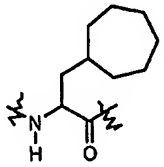
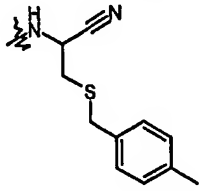
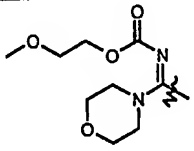
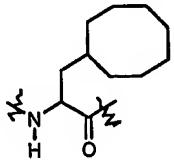
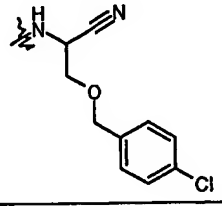
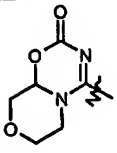
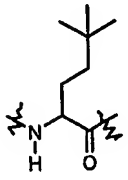
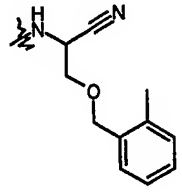


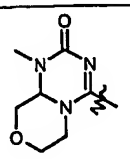
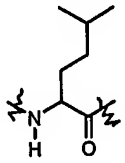
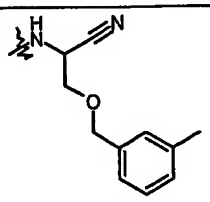
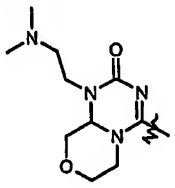
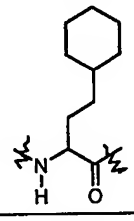
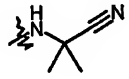
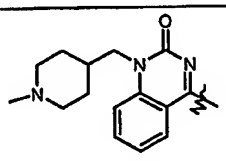
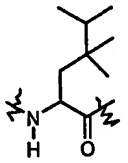
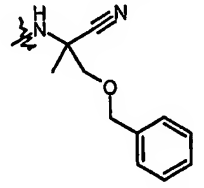
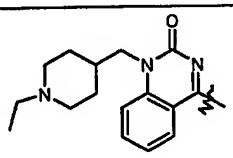
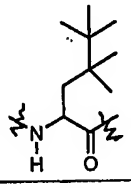
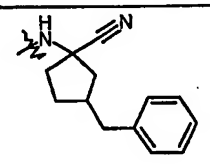
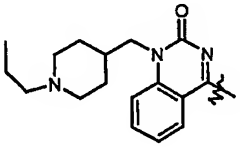
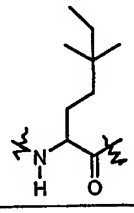
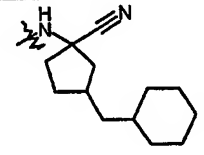
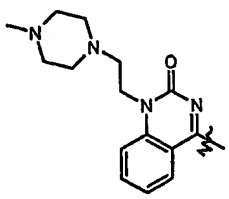
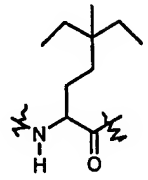
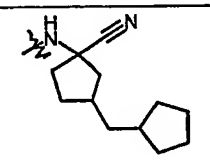
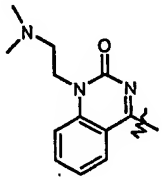
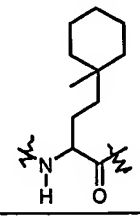
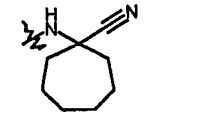
are chosen from any combination of A, B and C as follows:

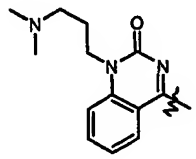
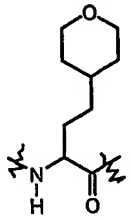
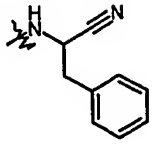
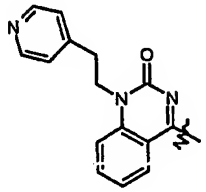
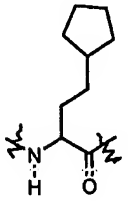
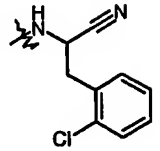
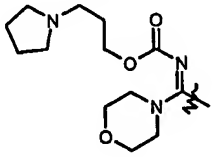
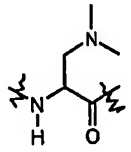
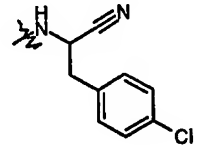
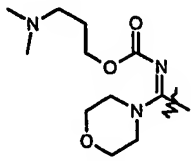
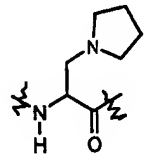
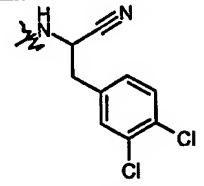
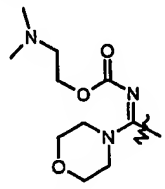
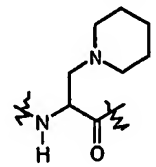
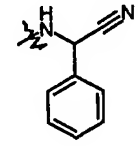
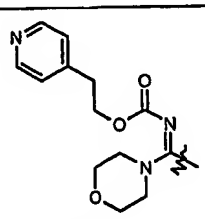
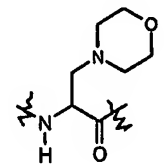
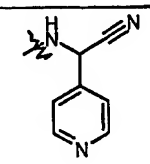
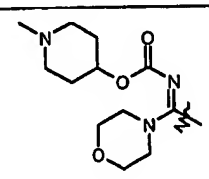
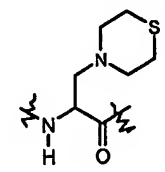
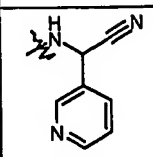
TABLE II

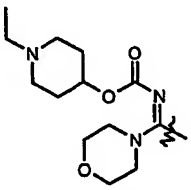
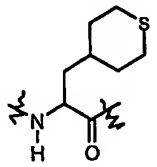
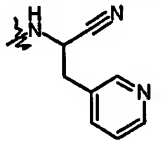
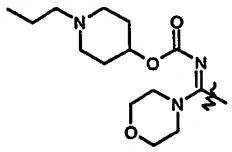
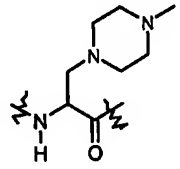
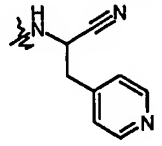
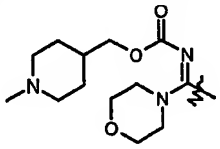
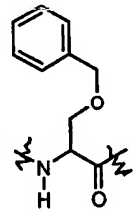
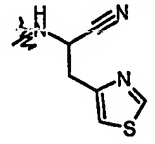
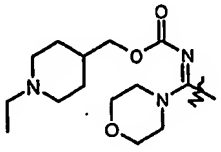
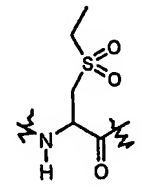
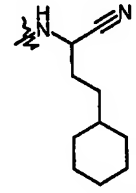
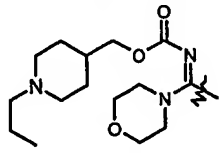
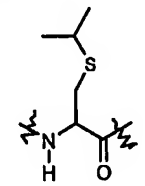
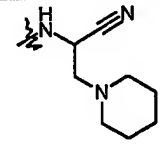
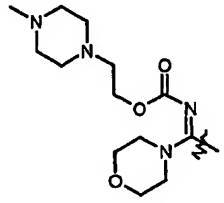
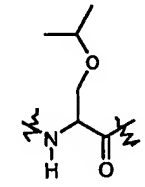
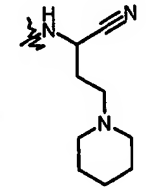
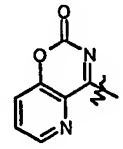
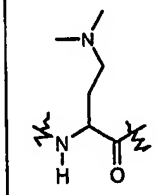
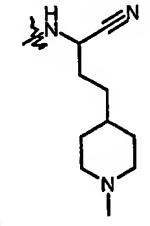
A		B		C	
A1		B1		C1	
A2		B2		C2	

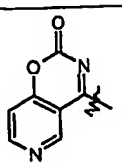
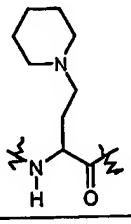
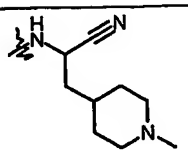
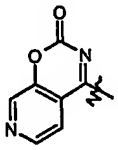
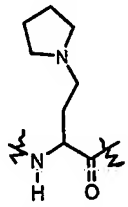
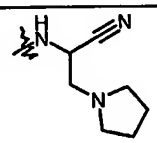
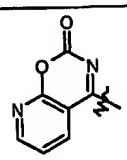
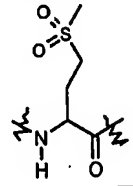
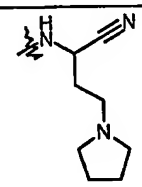
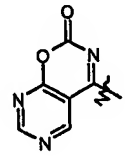
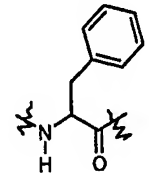
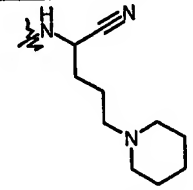
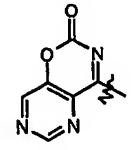
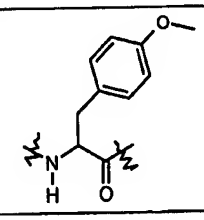
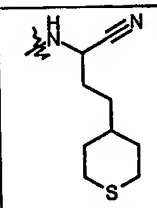
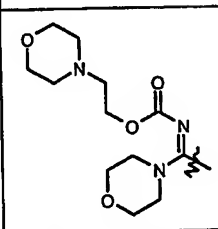
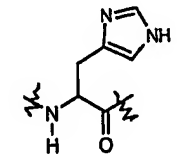
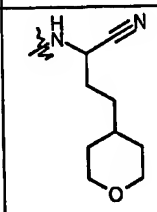
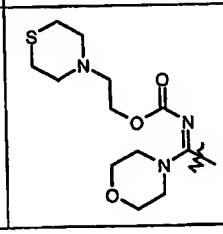
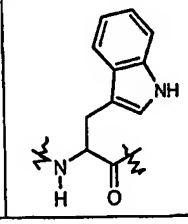
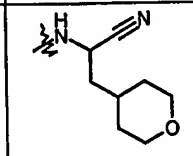
A3		B3		C3	
A4		B4		C4	
A5		B5		C5	
A6		B6		C6	
A7		B7		C7	
A8		B8		C8	
A9		B9		C9	

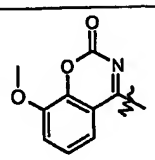
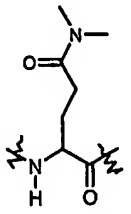
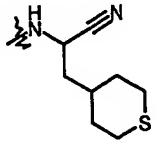
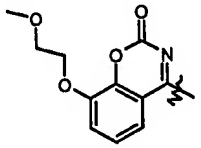
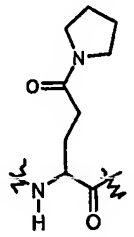
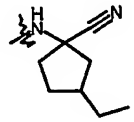
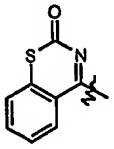
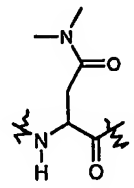
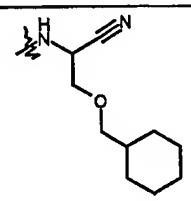
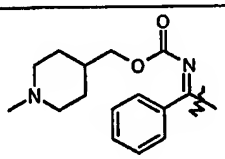
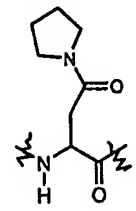
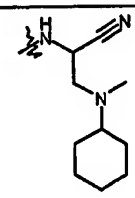
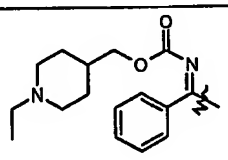
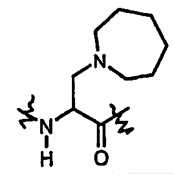
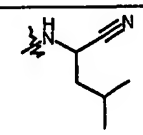
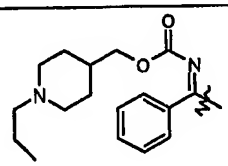
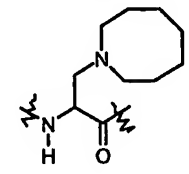
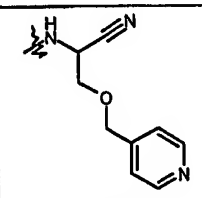
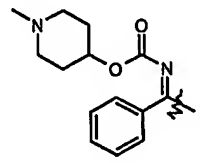
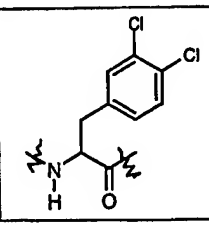
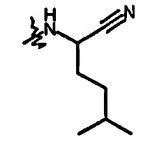
A10		B10		C10	
A11		B11		C11	
A12		B12		C12	
A14		B14		C14	
A15		B15		C15	
A16		B16		C16	

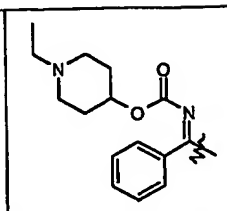
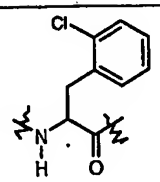
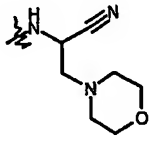
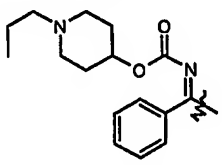
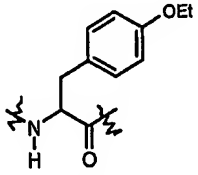
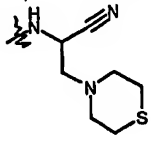
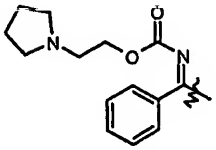
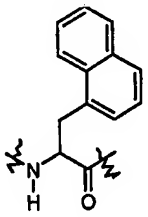
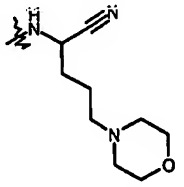
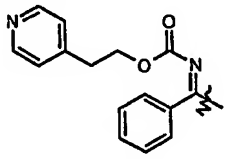
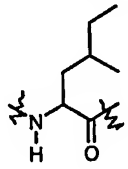
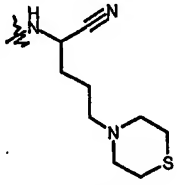
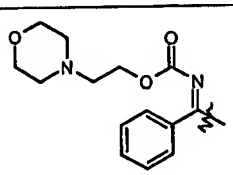
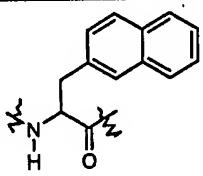
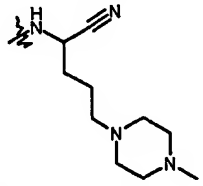
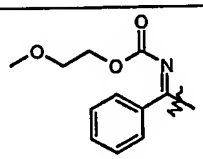
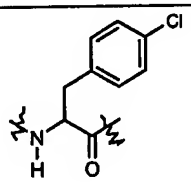
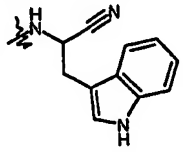
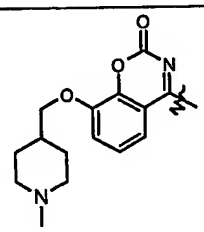
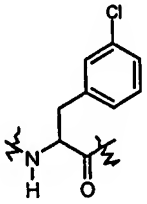
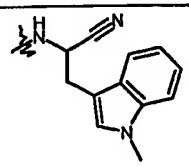
A17		B17		C17	
A18		B18		C18	
A19		B19		C19	
A20		B20		C20	
A21		B21		C21	
A22		B22		C22	
A23		B23		C23	

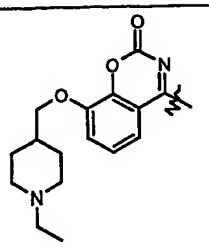
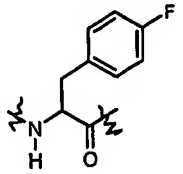
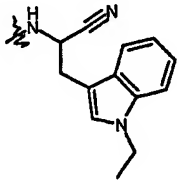
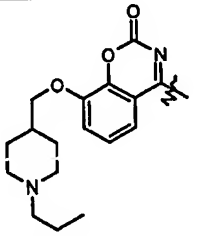
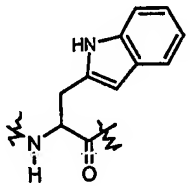
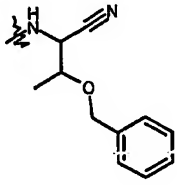
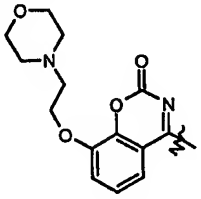
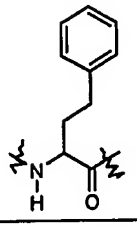
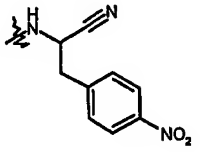
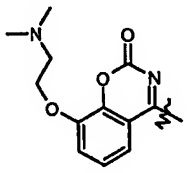
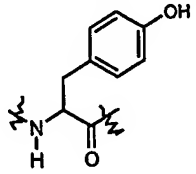
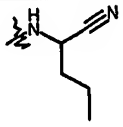
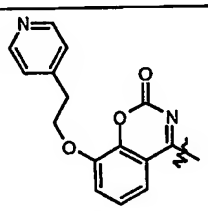
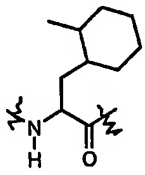
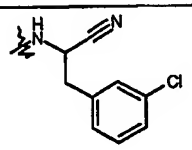
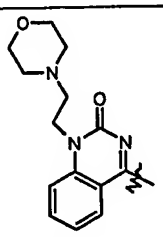
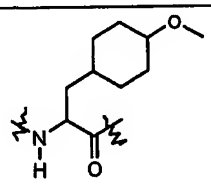
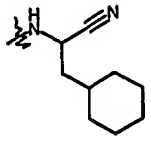
A24		B24		C24	
A25		B25		C25	
A26		B26		C26	
A27		B27		C27	
A28		B28		C28	
A29		B29		C29	
A30		B30		C30	

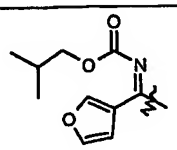
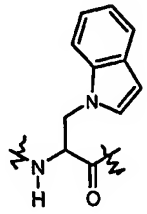
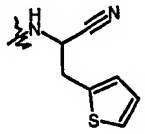
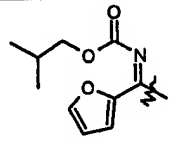
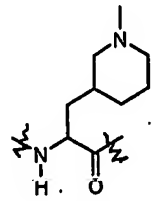
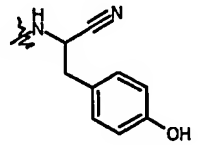
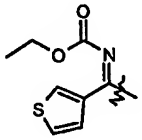
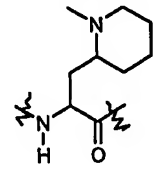
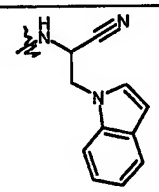
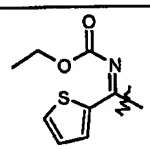
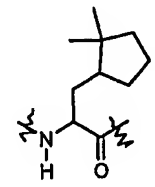
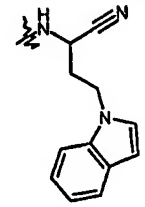
A31		B31		C31	
A32		B32		C32	
A33		B33		C33	
A34		B34		C34	
A35		B35		C35	
A36		B35		C36	
A37		B37		C37	

A38		B38		C38	
A39		B39		C39	
A40		B40		C40	
A41		B41		C41	
A42		B42		C42	
A43		B43		C43	
A44		B44		C44	

A45		B45		C45	
A46		B46		C46	
A47		B47		C47	
A48		B48		C48	
A49		B49		C49	
A50		B50		C50	
A51		B51		C51	

A52		B52		C52	
A53		B53		C53	
A54		B54		C54	
A55		B55		C55	
A56		B56		C56	
A57		B57		C57	
A58		B58		C58	

A59		B59		C59	
A60		B60		C60	
A61		B61		C61	
A62		B62		C62	
A63		B63		C63	
A64		B64		C64	

A65		B65		C65	
A66		B66		C66	
A67		B67		C67	
A68		B68		C68	

and the pharmaceutically acceptable derivates thereof.

The following subgeneric aspect of the compounds of the formulas (Ia) or (Ib) is postulated to possess Cathepsin K activity:

The broadest embodiment of the formula (Ia) or (Ib) as described hereinabove and wherein

R_1 is a bond, C1-4 alkyl, C1-4 alkoxy, cyclopropyl, cyclohexyl, phenoxy, naphthyloxy, phenyl, benzyl, naphthyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, furanyl, thienyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, indolyl, quinolinyl, benzofuranyl, benzthienyl, benzimidazolyl,

benzthiazolyl, benzoxazolyl or amino; wherein R_1 is optionally substituted by one or more R_a;

R_a is methyl, ethyl, propyl, i-propyl, cyclopropyl, cyclohexyl, phenyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, thienyl, imidazolyl, methoxy, ethoxy, acetyl, acetoxy, phenoxy, naphthyloxy, benzyloxy, methoxycarbonyl, ethoxycarbonyl, phenoxycarbonyl, naphthyloxycarbonyl, benzoyloxy, carbamoyl wherein the nitrogen atom may be independently mono or di-substituted by methyl, ethyl, phenyl, naphthyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl or piperazinyl,
or R_a is acetylamino, benzoylamino, methylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, ethylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, phenylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, ureido wherein either nitrogen atom may be independently substituted by methyl, ethyl, phenyl, naphthyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl or piperazinyl,
or R_a is methoxycarbonylamino, ethoxycarbonylamino, phenoxycarbonylamino, C1-2 alkylcarbamoyloxy, phenylcarbamoyloxy, naphthylcarbamoyloxy, C1-2 alkylsulfonylamino, phenylsulfonylamino, naphthylsulfonylamino, C1-2 alkylaminosulfonyl, phenylaminosulfonyl, naphthylaminosulfonyl, amino wherein the nitrogen atom may be independently mono or di-substituted by methyl, ethyl, phenyl, naphthyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl or piperazinyl,
or R_a is halogen, hydroxy, oxo, carboxy, cyano, nitro, carboxamide, amidino or guanidino, R_a may be further optionally substituted by one or more R_b;

R_b is methyl, ethyl, cyclopropyl, cyclohexyl, phenyl, methoxy, ethoxy, phenoxy, benzyloxy, fluoro, chloro, bromo, hydroxy, oxo, carboxy, cyano, nitro or carboxamide;

R_2 is hydrogen or methyl;

R_3 is a bond, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, n-pentyl, propenyl, i-butenyl, cyclohexyl, benzyl or naphthylmethyl wherein R_3 is optionally substituted by one or more R_c;

R_c is methyl, ethyl, cyclohexyl, cyclopentyl, phenyl, naphthyl, bicyclo[3.1.0]hexanyl, bicyclo[1.1.1]pentanyl, cubanyl, furanyl, tetrahydropyranyl, thienyl, oxazolyl, thiazolyl, imidazolyl, pyrimidinyl, methoxy, ethoxy, phenoxy, acetyl, benzoyl, methoxycarbonyl, phenoxycarbonyl, acetoxy, benzoyloxy,
or R_c is acetylamino, benzoylamino, methylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, phenylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone,
or R_c is phenoxycarbonylamino, phenylcarbamoyloxy, phenylsulfonylamino, phenylaminosulfonyl, amino wherein the nitrogen atom may be independently mono or di-substituted by methyl or phenyl,
or R_c is chloro, fluoro, hydroxy, oxo, carboxy or cyano;

R_2 and R_3 together with the carbon they are attached optionally form a ring selected from cyclopentyl, cyclohexyl, cycloheptyl, tetrahydropyranyl, tetrahydrothiopyranyl, tetrahydrofuranyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl or tetrahydrothiophenyl;

R_4 is hydrogen;
R_5 is hydrogen or C1-3alkyl;

R_9 is hydrogen, C1-12 alkyl wherein one or more carbon atoms are optionally replaced by O, S or N, phenyl or cyano, wherein R_9 is optionally substituted by one or more R_e;

R_e is selected from C1-3 alkyl, C3-6 cycloalkyl, phenyl, naphthyl, furanyl, thienyl, thiazolyl, imidazolyl, pyridinyl, indolyl, halogen, hydroxy, oxo, carboxy and cyano, R_e may be further optionally substituted by one or more R_f;

R_f is selected from C1-3 alkyl, phenyl optionally substituted by one or more groups selected from halogen and methyl, heterocyclyl selected from piperidinyl, morpholinyl and piperazinyl; heteroaryl selected from furanyl, thienyl, pyrrolyl and pyridinyl, C1-3 alkoxy, aryloxy, benzyloxy, C1-5 alkoxycarbonyl, C1-5 alkanoyloxy, aroyloxy, carbamoyl wherein the nitrogen atom may be independently mono or di-substituted by C1-5 alkyl or phenyl, C1-5 alkanoylamino, aroylamino, C1-5 alkylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, ureido wherein either nitrogen atom may be independently substituted by C1-5 alkyl or phenyl, C1-5 alkoxycarbonylamino, C1-5 alkylcarbamoyloxy, arylcarbamoyloxy, C1-3 alkylsulfonylamino, arylsulfonylamino, C1-3 alkylaminosulfonyl, arylaminosulfonyl, amino wherein the nitrogen atom may be independently mono or di-substituted by C1-3 alkyl or phenyl, halogen, hydroxy, oxo, carboxy and cyano;

or R_5 and R_9 together with the carbon they are attached form a carbocyclic ring of 3 to 5 carbon atoms, the carbocyclic ring being optionally substituted with one or more R_g;

R_g is selected from C1-3 alkyl, phenyl, C1-3 alkoxycarbonyl, benzyloxy, carbamoyl wherein the nitrogen atom may be optionally mono or di-substituted with a group selected from C1-5 alkyl, phenyl and benzyl, halogen, hydroxy, carboxy and cyano.

Preferred cathepsin K inhibitors are those as described immediately above and wherein:

R_1 is a bond, methyl, ethyl, n-propyl, i-propyl, methoxy, ethoxy, benzyloxy, cyclopropyl, cyclohexyl, phenoxy, naphthyloxy, phenyl, benzyl, naphthyl, pyrrolidinyl, piperidinyl,

morpholinyl, thiomorpholinyl, piperazinyl, furanyl, thienyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, indolyl, quinolinyl, benzofuranyl, benzthienyl, benzimidazolyl, benzthiazolyl, benzoxazolyl or amino; wherein R_1 is optionally substituted by one or more R_a;

R_a is methyl, cyclopropyl, phenyl, halogen, hydroxy, oxo, carboxy, cyano, nitro or carboxamide;

R_3 is a bond, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, n-pentyl, propenyl, i-butenyl, benzyl or naphthylmethyl wherein R_3 is optionally substituted by one or more R_c;

R_c is methyl, ethyl, cyclohexyl, cyclopentyl, phenyl, furanyl, tetrahydropyranyl, thienyl, oxazolyl, thiazolyl, methoxy, phenoxy, acetyl, benzoyl, methoxycarbonyl, or R_c is acetylamino, benzoylamino, methylthio, amino wherein the nitrogen atom may be independently mono or di-substituted by methyl,
or R_c is fluoro or oxo;

R_2 and R_3 together with the carbon they are attached optionally form a ring selected from cyclopentyl, cyclohexyl, cycloheptyl, tetrahydropyranyl, tetrahydrothiopyranyl, tetrahydrofuranyl, pyrrolidinyl or piperidinyl;

R_5 is hydrogen or methyl;

R_9 is hydrogen, C1-12 alkyl wherein one or more carbon atoms are optionally replaced by O, S or N, phenyl or cyano wherein R_9 is optionally substituted by one or more groups of the formula R_e;

R_e is selected from methyl, C3-6 cycloalkyl, phenyl, naphthyl, furanyl, thienyl, thiazolyl, imidazolyl, pyridinyl, indolyl, halogen, hydroxy, oxo, carboxy and cyano, R_e may be further optionally substituted by one or more R_f.

R_f is selected from C1-3 alkyl, phenyl optionally substituted by one or more groups selected from halogen or methyl, C1-3 alkoxy, aryloxy, benzyloxy, C1-3 alkoxycarbonyl, carbamoyl wherein the nitrogen atom may be independently mono or di-substituted by C1-3 alkyl or phenyl, C1-5 alkanoylamino, aroylamino, amino wherein the nitrogen atom may be independently mono or di-substituted by C1-3 alkyl or phenyl, halogen, hydroxy, oxo, carboxy and cyano;

or R_5 and R_9 together with the carbon they are attached form a carbocyclic ring of 3 to 5 carbon atoms, the carbocyclic ring being optionally substituted with one or more R_g;

R_g is selected from C1-3 alkyl, phenyl, C1-3 alkoxycarbonyl, benzyloxy and carboxy.

Most preferred cathepsin K inhibitors are those as described immediately above and wherein:

R_1 is methoxy, benzyloxy, cyclohexyl, phenoxy, naphthyloxy, phenyl, benzyl, naphthyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, furanyl, thienyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, quinolinyl, benzofuranyl, benzthienyl, benzimidazolyl, benzthiazolyl, benzoxazolyl or amino; wherein R_1 is optionally substituted by one or more R_a;

R_a is methyl, phenyl, fluoro, chloro, hydroxy, oxo, carboxy or carboxamide;

R_3 is a bond, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, n-pentyl, propenyl, i-butenyl or benzyl wherein R_3 is optionally substituted by one or more R_c;

R_c is methyl, ethyl, cyclohexyl, cyclopentyl, phenyl, furanyl, tetrahydropyranyl, thienyl, oxazolyl, thiazolyl, methoxy, phenoxy, acetyl, benzoyl, methoxycarbonyl, acetylamino, methylthio or fluoro;

R_2 and R_3 together with the carbon they are attached optionally form a ring selected from cyclopentyl, cyclohexyl, cycloheptyl, tetrahydropyranyl, tetrahydrothiopyranyl or tetrahydrofuranyl;

R_9 is hydrogen, C1-5 alkyl, C1-5 alkylene, C1-5 alkoxyC1-5 alkyl, C1-5 alkoxycarbonylC1-5 alkyl, C1-5 alkylthioC1-5 alkyl, C1-5 alkylthiosulfoneC1-5 alkyl, C1-5 alkylthiosulfonylC1-5 alkyl, aminoC1-5 alkyl, mono or di-C1-5alkylaminoC1-5 alkyl, mono or di-C1-5 alkylamidoC1-5 alkyl or phenyl, wherein R_9 is optionally substituted by one or more R_e;

R_e is selected from C3-6 cycloalkyl, phenyl, naphthyl, thienyl, imidazolyl, pyridinyl, indolyl, halogen, hydroxy, carboxy and cyano, R_e may be further optionally substituted by one or more R_f;

R_f is selected from methyl, phenyl optionally substituted by one or more groups selected from halogen or methyl, methoxy, phenoxy, benzyloxy, methoxycarbonyl, amino wherein the nitrogen atom may be independently mono or di-substituted by C1-3 alkyl or phenyl, halogen, hydroxy and carboxy;

or R_5 and R_9 together with the carbon they are attached form a carbocyclic ring of 3 to 5 carbon atoms, the carbocyclic ring being optionally substituted with one or more R_g;

R_g is selected from phenyl, methoxycarbonyl, benzyloxycarbonyl and carboxy.

Most preferred cathepsin K inhibitors are those as described immediately above and wherein:

R_1 is benzyloxy, phenoxy, naphthyloxy, phenyl, naphthyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, pyridinyl, indolyl, quinolinyl, benzofuranyl, benzthienyl, benzimidazolyl, benzthiazolyl, benzoxazolyl or phenylamino;

R_3 is n-propyl, i-butyl, propenyl, i-butenyl or 2,2-dimethylpropyl;

R_2 and R_3 together with the carbon they are attached optionally form a ring selected from cyclopentyl, cyclohexyl, or cycloheptyl;

R_5 is hydrogen;

R_e is selected from C5-6 cycloalkyl, phenyl, naphthyl, thienyl, indolyl, halogen, hydroxy, carboxy and cyano, R_f may be further optionally substituted by one or more R_f;

R_f is selected from methyl, phenyl optionally substituted by halogen, methoxy, phenoxy, benzyloxy, methoxycarbonyl, halogen, hydroxy and carboxy;

or R_5 and R_9 together with the carbon they are attached form a carbocyclic ring of 3 carbon atoms, the carbocyclic ring being optionally substituted with one or more R_g;

R_g is phenyl.

Even more preferred cathepsin K inhibitors are those as described immediately above and wherein:

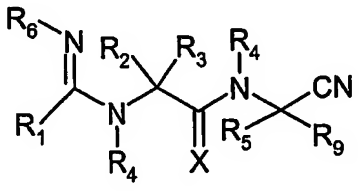
R_e is selected from C5-6 cycloalkyl, phenyl, naphthyl, indolyl, halogen and carboxy, R_f may be further optionally substituted by one or more R_f;

R_f is selected from methyl, methoxy, methoxycarbonyl, halogen and hydroxy, and

R_5 and R_9 together with the carbon they are attached form a carbocyclic ring of 3 carbon atoms, the carbocyclic ring being optionally substituted with one or more R_8.

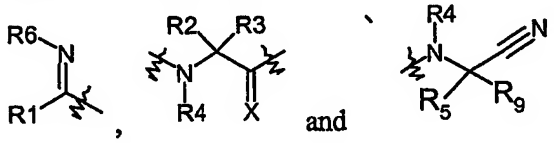
Further compounds of Formula (Ia), made up of components A, B, and C are provided in Table III below. Any and all combinations of A, B, and C components within the structural limitations of Formula (Ia), comprise a compound of the invention preferably possessing CAT K activity.

FORMULA (Ia)



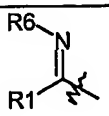
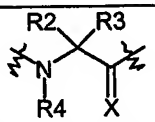
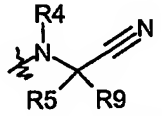
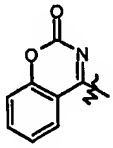
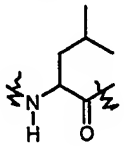
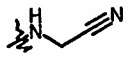
(Ia)

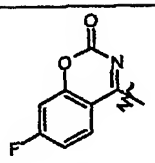
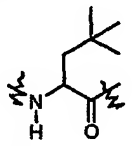
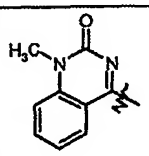
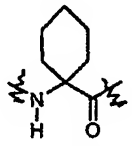
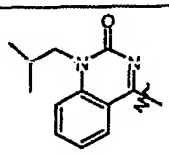
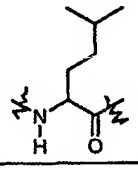
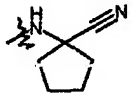
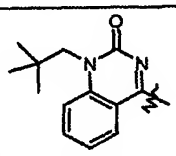
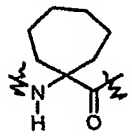
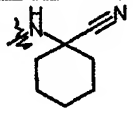
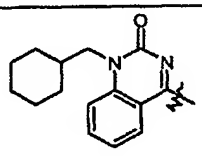
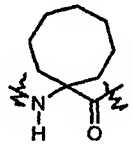
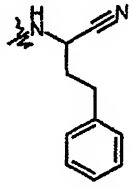
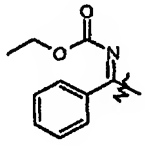
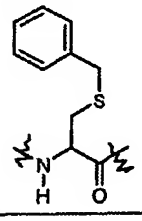
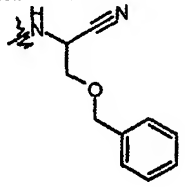
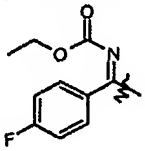
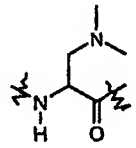
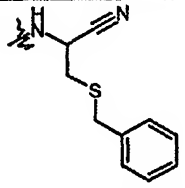
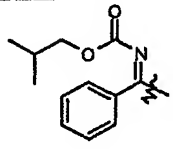
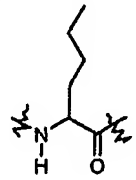
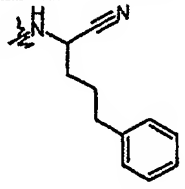
wherein for the Formula (Ia), the components

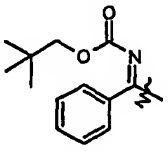
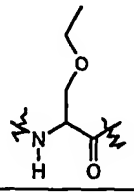
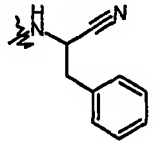
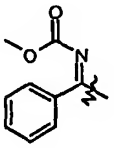
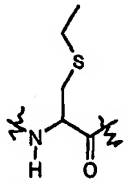
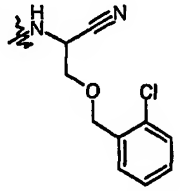
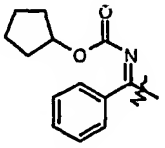
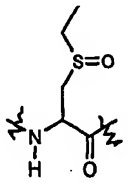
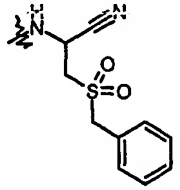
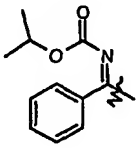
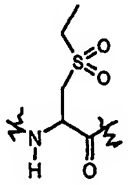
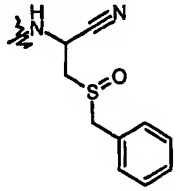
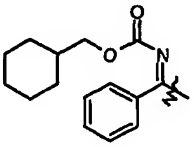
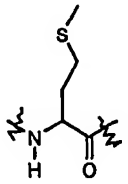
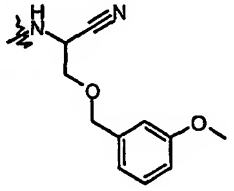
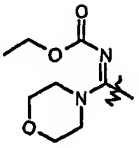
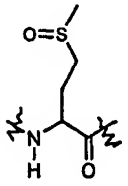
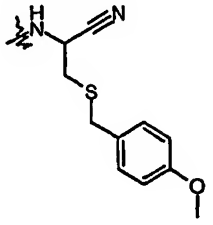
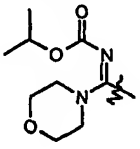
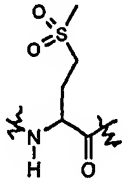
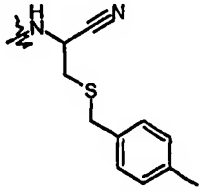


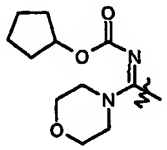
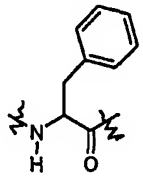
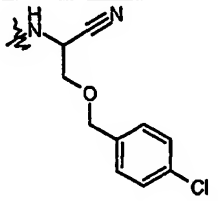
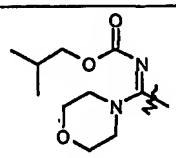
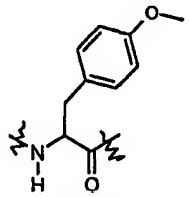
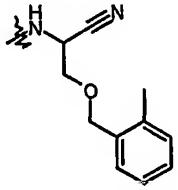
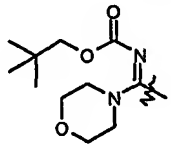
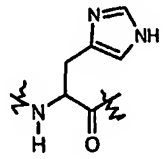
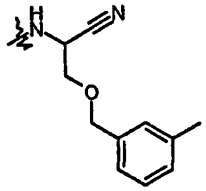
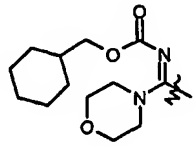
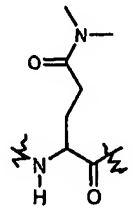
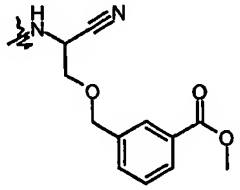
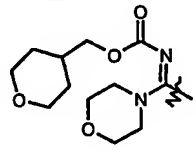
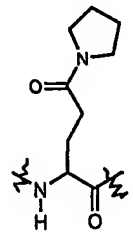
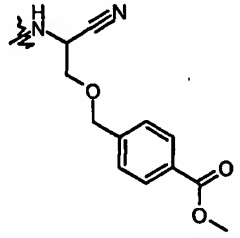
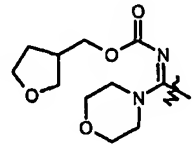
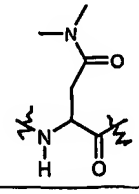
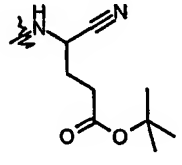
are chosen from any combination of A, B and C as follows:

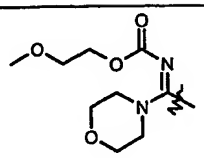
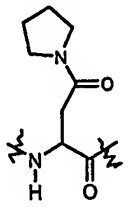
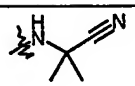
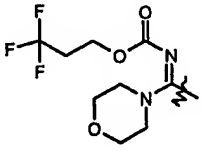
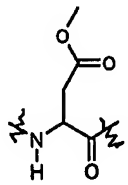
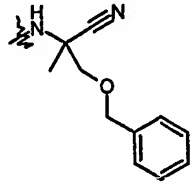
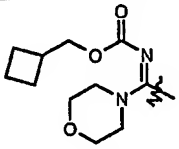
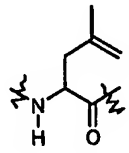
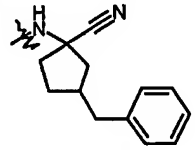
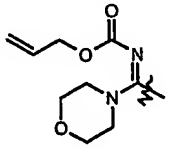
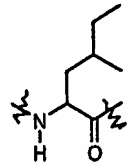
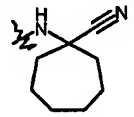
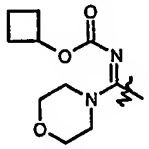
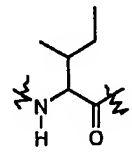
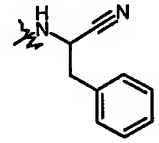
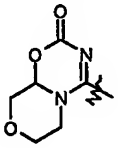
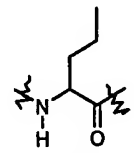
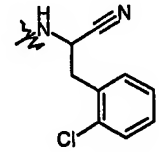
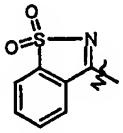
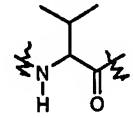
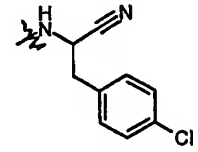
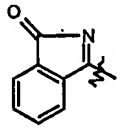
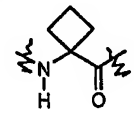
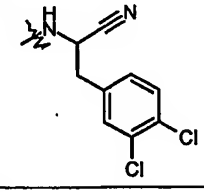
TABLE III

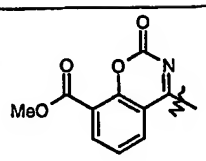
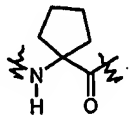
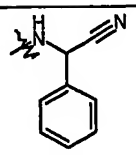
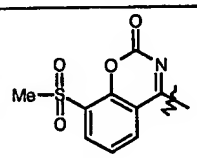
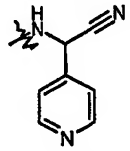
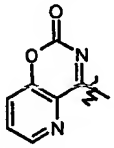
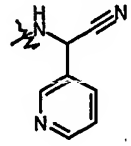
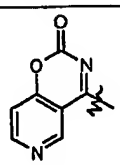
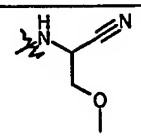
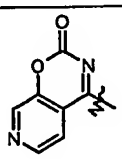
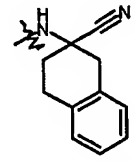
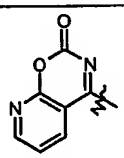
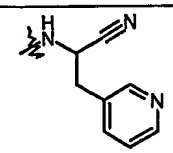
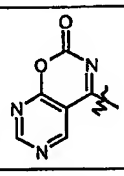
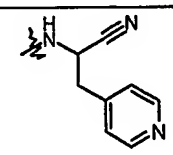
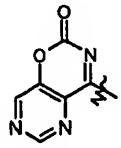
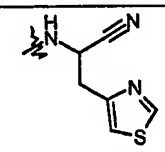
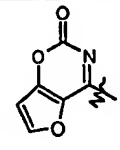
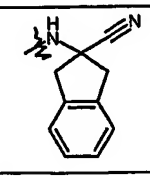
A		B		C	
A1		B1		C1	

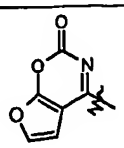
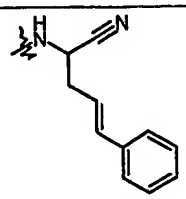
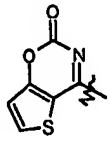
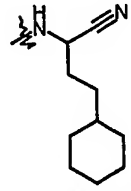
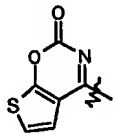
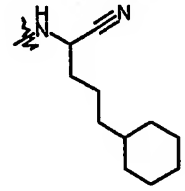
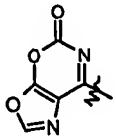
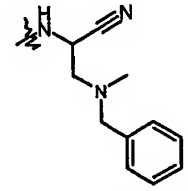
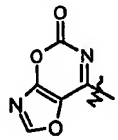
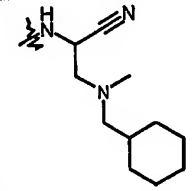
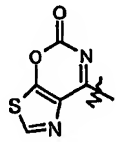
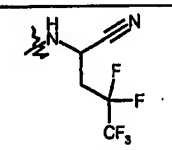
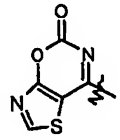
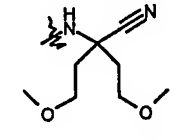
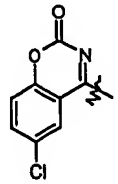
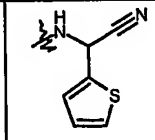
A2		B2		C2	
A3		B3		C3	
A4		B4		C4	
A5		B5		C5	
A6		B6		C6	
A7		B7		C7	
A8		B8		C8	
A9		B9		C9	

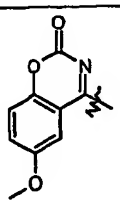
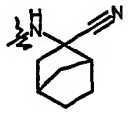
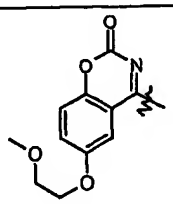
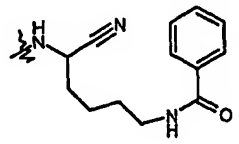
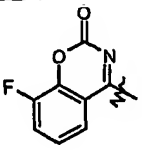
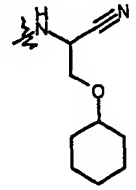
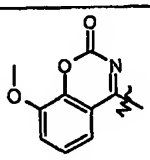
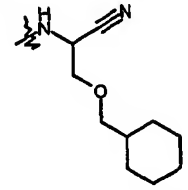
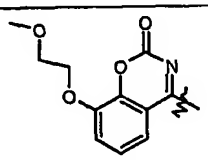
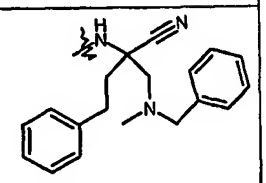
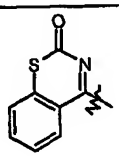
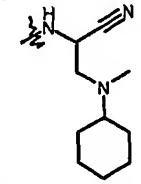
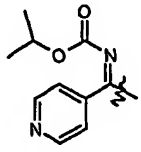
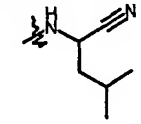
A10		B10		C10	
A11		B11		C11	
A12		B12		C12	
A13		B13		C13	
A14		B14		C14	
A15		B15		C15	
A16		B16		C16	

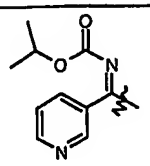
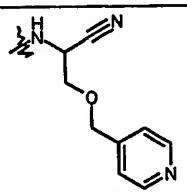
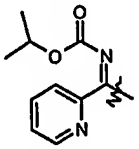
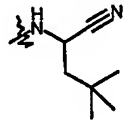
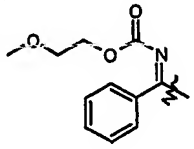
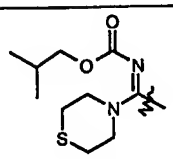
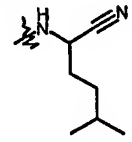
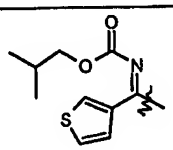
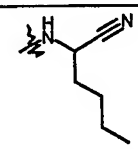
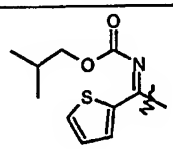
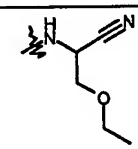
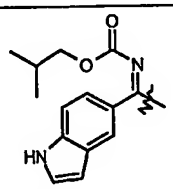
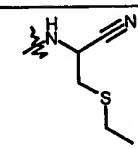
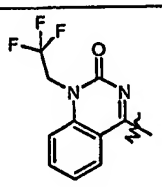
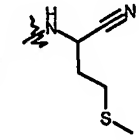
A17		B17		C17	
A18		B18		C18	
A19		B19		C19	
A20		B20		C20	
A21		B21		C21	
A22		B22		C22	

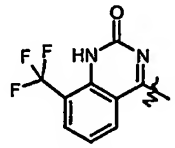
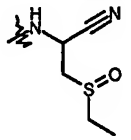
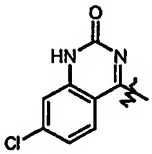
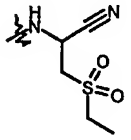
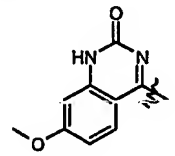
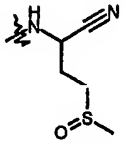
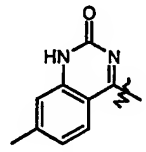
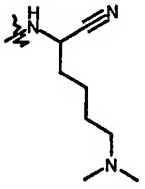
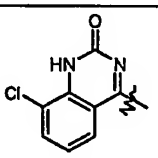
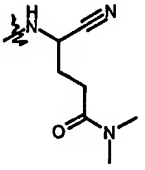
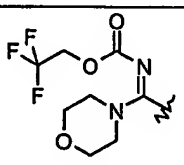
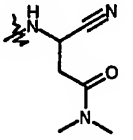
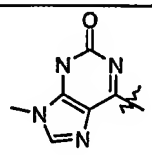
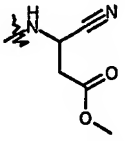
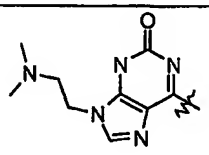
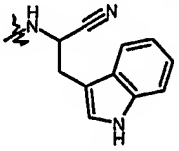
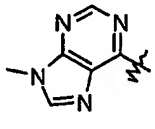
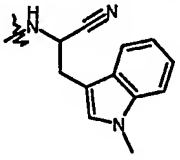
A23		B23		C23	
A24		B24		C24	
A25		B25		C25	
A26		B26		C26	
A27		B27		C27	
A28		B28		C28	
A29		B29		C29	
A30		B30		C30	

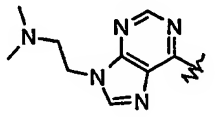
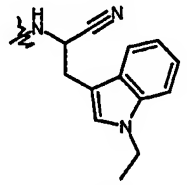
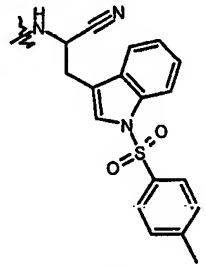
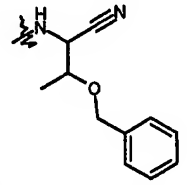
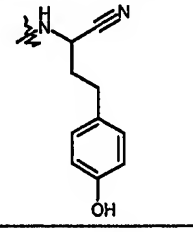
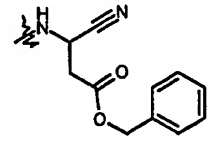
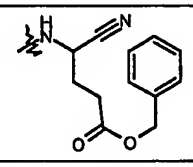
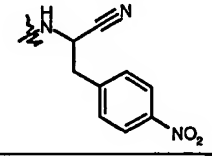
A31		B31		C31	
A32				C32	
A33				C33	
A34				C34	
A35				C35	
A36				C36	
A37				C37	
A38				C38	
A39				C39	

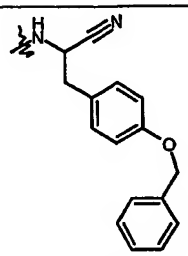
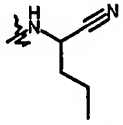
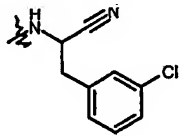
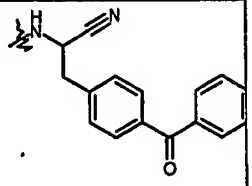
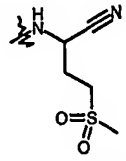
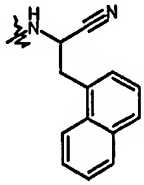
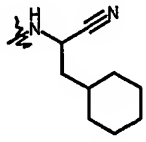
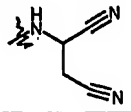
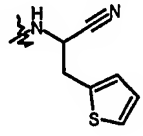
A40				C40	
A41				C41	
A42				C42	
A43				C43	
A44				C44	
A45				C45	
A46				C46	
A47				C47	

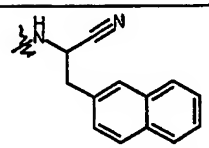
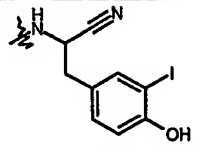
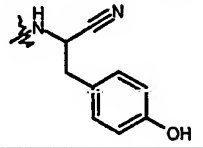
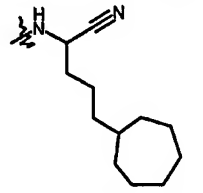
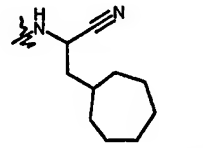
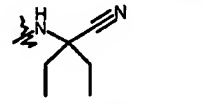
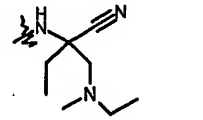
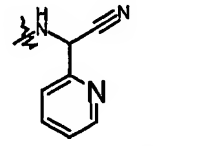
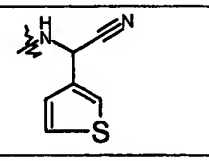
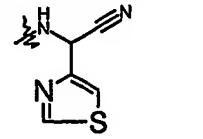
A48				C48	
A49				C49	
A50				C50	
A51				C51	
A52				C52	
A53				C53	
A54				C54	

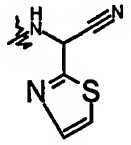
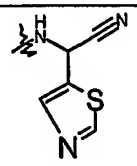
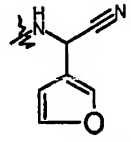
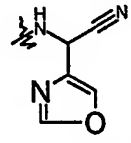
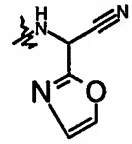
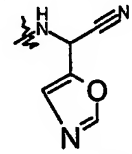
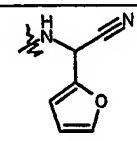
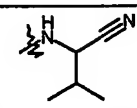
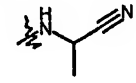
A55				C55	
A56				C56	
A57				C57	
A58				C58	
A59				C59	
A60				C60	
A61				C61	
A62				C62	

A63				C63	
A64				C64	
A65				C65	
A66				C66	
A67				C67	
A68				C68	
A69				C69	
A70				C70	
A71				C71	

A72				C72	
				C73	
				C74	
				C75	
				C76	
				C77	
				C78	

				C79	
				C80	
				C81	
				C82	
				C83	
				C84	
				C85	
				C86	
				C87	

				C88	
				C89	
				C90	
				C91	
				C92	
				C93	
				C94	
				C95	
				C96	
				C97	

				C98	
				C99	
				C100	
				C101	
				C102	
				C103	
				C104	
				C105	
				C106	

and the pharmaceutically acceptable derivates thereof.

5

For all the compounds disclosed in this application, in the event the nomenclature is in conflict with the structure, it shall be understood that the compound is defined by the structure.

Any compounds of this invention containing one or more asymmetric carbon atoms may occur as racemates and racemic mixtures, single enantiomers, diastereomeric mixtures and individual diastereomers. All such isomeric forms of these compounds are expressly included in the present invention. Each stereogenic carbon may be in the R or S configuration unless otherwise specified, or a combination of configurations.

Some of the compounds can exist in more than one tautomeric form. The invention includes all such tautomers.

It shall be understood by one of ordinary skill in the art that all compounds of the invention are those which are chemically stable.

The invention includes pharmaceutically acceptable derivatives of compounds of formula (Ia/Ib). A "pharmaceutically acceptable derivative" refers to any pharmaceutically acceptable acid, salt or ester of a compound of this invention, or any other compound which, upon administration to a patient, is capable of providing (directly or indirectly) a compound of this invention, a pharmacologically active metabolite or pharmacologically active residue thereof.

In addition, the compounds of this invention include prodrugs of compounds of the formula (I/Ib). Prodrugs include those compounds that, upon simple transformation, are modified to produce the compounds of the invention. Simple chemical transformations include hydrolysis, oxidation and reduction which occur enzymatically, metabolically or otherwise. Specifically, when a prodrug of this invention is administered to a patient, the prodrug may be transformed into a compound of formula (Ia/Ib) , thereby imparting the desired pharmacological effect.

In order that the invention herein described may be more fully understood, the following detailed description is set forth. As used herein, the following abbreviations are used:

BOC or t-BOC is tertiary-butoxycarbonyl;
t-Bu is tertiary-butyl;
DMF is dimethylformamide;
EtOAc is ethyl acetate;
THF is tetrahydrofuran;
Ar is argon;
EDC is 1-(3-dimethylaminopropyl)-3-ethylcarbodimide hydrochloride and
HOBT is 1-hydroxybenzotriazole.

Also, as used herein, each of the following terms, used alone or in conjunction with other terms, are defined as follows (except where noted to the contrary):

The term "alkyl" refers to a saturated aliphatic radical containing from one to ten carbon atoms or a mono- or polyunsaturated aliphatic hydrocarbon radical containing from two to twelve carbon atoms. The mono- or polyunsaturated aliphatic hydrocarbon radical containing at least one double or triple bond, respectively. "Alkyl" refers to both branched and unbranched alkyl groups. Examples of "alkyl" include alkyl groups which are straight chain alkyl groups containing from one to eight carbon atoms and branched alkyl groups containing from three to eight carbon atoms. Other examples include lower alkyl groups which are straight chain alkyl groups containing from one to six carbon atoms and branched alkyl groups containing from three to six carbon atoms. It should be understood that any combination term using an "alk" or "alkyl" prefix refers to analogs according to the above definition of "alkyl". For example, terms such as "alkoxy", "alkythio" refer to alkyl groups linked to a second group via an oxygen or sulfur atom. "Alkanoyl" refers to an alkyl group linked to a carbonyl group (C=O). Each alkyl or alkyl analog described herein shall be understood to be optionally partially or fully halogenated.

The term "cycloalkyl" refers to the cyclic analog of an alkyl group, as defined above. Examples of cycloalkyl groups are saturated or unsaturated nonaromatic cycloalkyl groups containing from three to eight carbon atoms, and other examples include cycloalkyl groups having three to six carbon atoms. Each cycloalkyl described herein shall be understood to be optionally partially or fully halogenated.

The term "aryl" refers to phenyl and naphthyl.

The term "halo" refers to a halogen radical selected from fluoro, chloro, bromo or iodo. Representative halo groups of the invention are fluoro, chloro and bromo.

The term "heteroaryl" refers to a stable 5-8 membered (but preferably, 5 or 6 membered) monocyclic or 8-11 membered bicyclic aromatic heterocycle radical. Each heterocycle consists of carbon atoms and from 1 to 4 heteroatoms chosen from nitrogen, oxygen and sulfur. The heterocycle may be attached by any atom of the cycle, which results in the creation of a stable structure. Examples of "heteroaryl" include radicals such as furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, tetrazolyl, thiadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, indolizinyl, indolyl, isoindolyl, benzofuranyl, benzothienyl, indazolyl, benzimidazolyl, benzthiazolyl, benzoxazolyl, benzoxazinyl, purinyl, quinolizinyl, quinolinyl, isoquinolinyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, naphthyridinyl, pteridinyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl and phenoxazinyl,

The term "heterocycle" refers to a stable 4-8 membered (but preferably, 5 or 6 membered) monocyclic or 8-11 membered bicyclic heterocycle radical which may be either saturated or unsaturated, and is non-aromatic. Each heterocycle consists of carbon atoms and from 1 to 4 heteroatoms chosen from nitrogen, oxygen and sulfur. The heterocycle may be attached by any atom of the cycle, which results in the creation of a stable structure. Examples of "heterocycle" include radicals such as pyrrolinyl,

pyrrolidinyl, pyrazolinyl, pyrazolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, pyranyl, thiopyranyl, piperazinyl, indolinyl, azetidinyl, tetrahydropyranyl, tetrahydrothiopyranyl, tetrahydrofuranyl, hexahydropyrimidinyl, hexahydropyridazinyl, 1,4,5,6-tetrahydropyrimidin-2-ylamine, dihydro-oxazolyl, 1,2-thiazinanyl-1,1-dioxide, 1,2,6-thiadiazinanyl-1,1-dioxide, isothiazolidinyl-1,1-dioxide and imidazolidinyl-2,4-dione.

The terms "heterocycle", "heteroaryl" or "aryl", when associated with another moiety, unless otherwise specified shall have the same meaning as given above. For example, "aroyl" refers to phenyl or naphthyl linked to a carbonyl group (C=O).

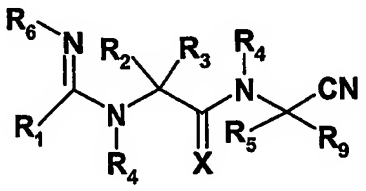
Each aryl or heteroaryl unless otherwise specified includes it's partially or fully hydrogenated derivative. For example, quinolinyl may include decahydroquinolinyl and tetrahydroquinolinyl, naphthyl may include it's hydrogenated derivatives such as tetrahydranaphthyl. Other partially or fully hydrogenated derivatives of the aryl and heteroaryl compounds described herein will be apparent to one of ordinary skill in the art.

In all alkyl groups or carbon chains where one or more carbon atoms are optionally replaced by heteroatoms: O, S or N, it shall be understood that if N is not substituted then it is NH, it shall also be understood that the heteroatoms may replace either terminal carbon atoms or internal carbon atoms within a branched or unbranched carbon chain. Such groups can be substituted as herein above described by groups such as oxo to result in defintions such as but not limited to: alkyl, alkylene, alkoxyalkyl, alkoxycarbonylalkyl, alkylthioalkyl, alkylthiosulfonealkyl, alkylthiosulfonylalkyl, amino alkyl, mono or di-alkylaminoalkyl, mono or di-alkylamidoC1-5 alkyl.

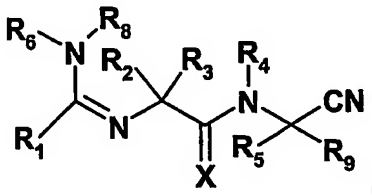
As used herein above and throughout this application, "nitrogen" and "sulfur" include any oxidized form of nitrogen and sulfur and the quaternized form of any basic nitrogen.

GENERAL SYNTHETIC METHODS

The invention also provides processes of making the present novel compounds of formula (Ia) and (Ib). Compounds of the invention may be prepared by methods described below, those found in US applications serial nos. 09/434,106, 09/627,869, 09/655,351 and 09/808,439 each incorporated herein in their entirety, and by methods known to those of ordinary skill in the art.

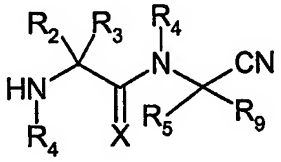


(Ia),



(Ib)

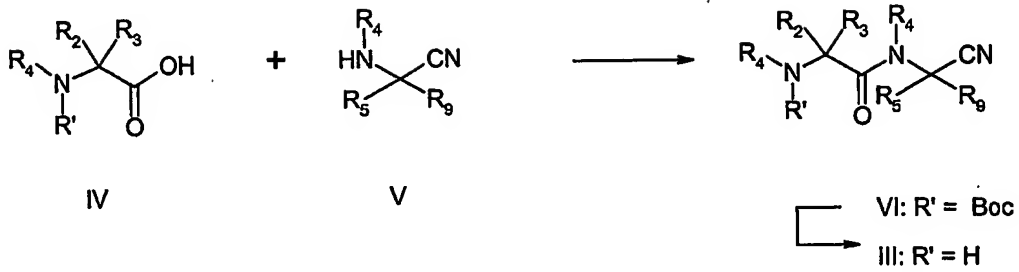
A key intermediate in the preparation of compounds of formula (Ia) and (Ib) is the dipeptide nitrile intermediate (III).



(III)

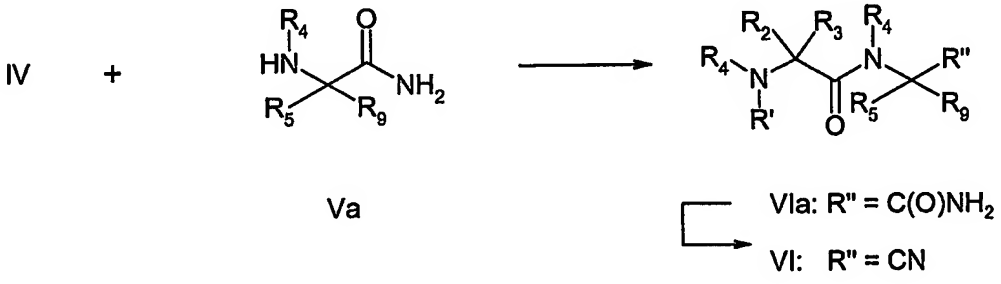
The synthesis of intermediates of formula (III) may be carried out by methods outlined below in Schemes I and II and methods described in the applications cited above.

Scheme I



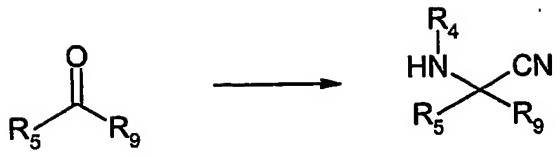
As illustrated in Scheme I, an amino acid bearing a suitable protecting group R' (IV), is reacted with an amino nitrile (V) under suitable coupling conditions. An example of a suitable protecting group is the *t*-butoxycarbonyl (BOC) group. An example of standard coupling conditions would be combining the starting materials in the presence of a coupling reagent such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDC) with 1-hydroxybenzotriazole (HOBT), in a suitable solvent such as DMF or methylene chloride. A base such as N-methylmorpholine may be added. This is followed by deprotection to give amino acid nitrile III.

In a variation of the above method, one may couple IV with an amino amide (Va) and convert the product VIa to nitrile VI by dehydration, for example with cyanuric chloride in DMF



The intermediate aminonitrile (V) used in Scheme I above may be prepared as outlined in Scheme II.

Scheme II

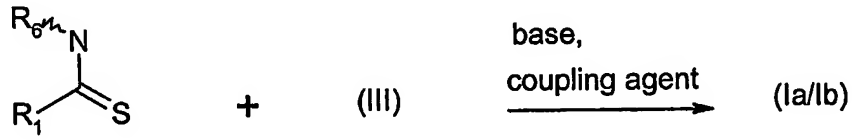


VII V

In this method, a ketone bearing R_5 and R_9 (VII) is reacted with an a primary amine or an ammonium salt, such as ammonium chloride, and a cyanide salt, such as potassium cyanide or sodium cyanide, in a suitable solvent, such as water or a solution of ammonia in methanol, at about room temperature to reflux temperature.

Compounds having formula (Ia/Ib) may be prepared by Methods A-D, as illustrated in Schemes III-VI.

Scheme III (Method A)

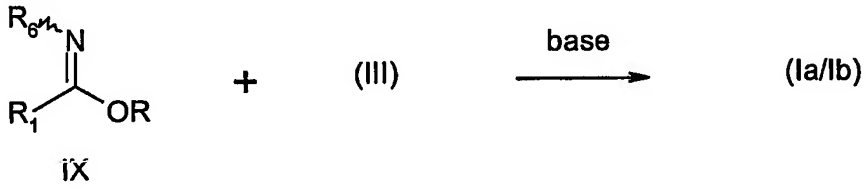


VIII

According to Method A, a dipeptide nitrile intermediate (III), or a basic salt thereof, is allowed to react with (VIII) in the presence of a suitable coupling agent to provide the desired product (Ia/Ib). Suitable reaction conditions are known to those skilled in the art and some examples of suitable coupling agents include 2-chloro-1-methylpyridinium iodide (Yong, Y.F. et al., J. Org. Chem. 1997, 62, 1540), phosgene or triphosgene (Barton, D.H. et al., J. Chem. Soc. Perkin Trans. I, 1982, 2085), alkyl halides (Brand, E. and Brand, F. C., Org. Synth., 1955, 3, 440) carbodiimides (Poss, M. A. et al., Tetrahedron Lett., 1992, 40, 5933) and mercury salts (Su, W., Synthetic Comm., 1996, 26, 407 and Wiggall, K. J. and Richardson, S. K. J., Heterocyclic Chem., 1995, 32, 867).

Compounds having formulas (Ia) and (Ib) may also be prepared by Method B as illustrated in Scheme IV, where R is an alkyl or aryl group.

Scheme IV (Method B)

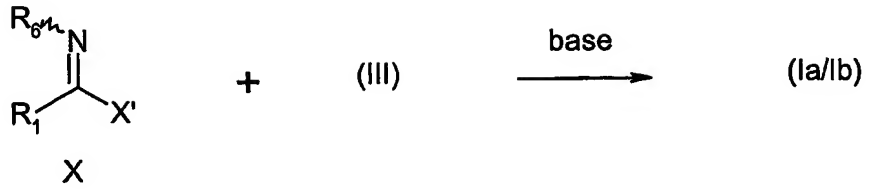


According to Method B a dipeptide nitrile intermediate (III), or a basic salt thereof, is allowed to react with IX, with or without an added base such as triethylamine, to provide the desired product (Ia/Ib). Suitable reaction conditions are known to those skilled in the art and examples of such amine additions may be found in the chemical literature, for example Haake, M. and Schummelfeder, B., Synthesis, 1991, 9, 753; Dauwe, C. and Buddrus, J., Synthesis 1995, 2, 171; Ried, W. and Piechaczek, D., Justus Liebigs Ann. Chem. 1966, 97, 696 and Dean, W. D. and Papadopoulos, E. P., J. Heterocyclic Chem., 1982, 19, 1117.

The intermediate IX is either commercially available or can be synthesized by methods known to those skilled in the art and described in the literature, for example Francesconi, I. et. al., J. Med. Chem. 1999, 42, 2260; Kurzer, F., Lawson, A.,Org. Synth. 1963, 645, and Gutman, A. D. US 3984410, 1976.

In a similar reaction, intermediate X having a halogen or other suitable leaving group (X') may be used in place of intermediate IX, as illustrated in Method C, Scheme V.

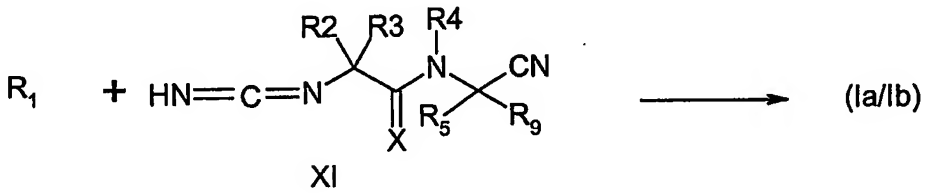
Scheme V (Method C)



According to Method C, a dipeptide nitrile intermediate, or a basic salt thereof, is allowed to react with intermediate X, with or without an added base such as triethylamine, to provide the desired product (Ia/Ib). Procedures for accomplishing this reaction are known to those skilled in the art and described in the chemical literature (for example, Dunn, A. D. , Org. Prep. Proceed. Int., 1998, 30, 709; Lindstroem, S. et al., Heterocycles, 1994, 38, 529; Katritzky, A. R. and Saczewski, F., Synthesis, 1990, 561; Hontz, A. C. and Wagner, E. C., Org Synth., 1963, IV, 383; Stephen, E. and Stephen, H., J. Chem. Soc., 1957, 490).

Compounds having formula (Ia/Ib) in which R_1 is an amine may also be prepared by Method D as illustrated in Scheme VI.

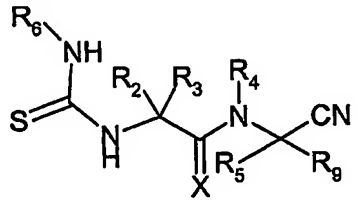
Scheme VI (Method D)



According to Method D, a carbodiimide (XI) derivative of (III) is allowed to react with an amine (R_1) to provide the desired guanidine (Ia/Ib) product. The conversion of amines to carbodiimides is known to those in the art and described in the literature (for example, Pri-Bar, I. and Schwartz, J., J. Chem. Soc. Chem. Commun., 1997, 347; Hirao, T. and Saegusa, T., J. Org. Chem., 1975, 40, 298). The reaction of carbodiimides with amine nucleophiles is also described in the literature (for example, Yoshiizumi, K. et al., Chem.

Pharm. Bull., 1997, 45, 2005; Thomas, E. W. et al., J. Med. Chem., 1989, 32, 228; Lawson, A. and Tinkler, R. B., J. Chem. Soc. C, 1971, 1429.

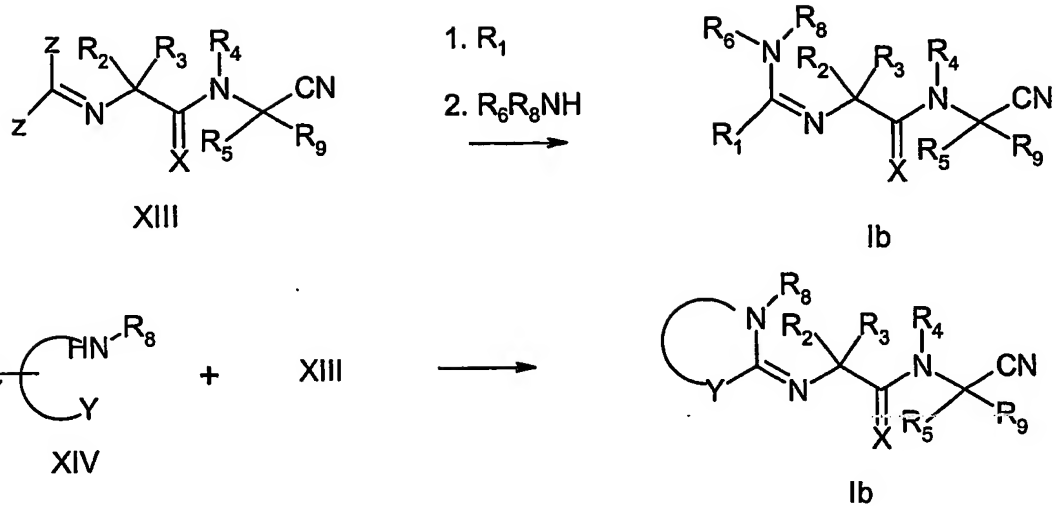
In a modification of Method D, one may start with the thiourea XII (formed by reaction of the corresponding amine with an isothiocyanate $R_6N=C=S$) and then form the corresponding carbodiimide (XI) *in situ* by reaction with a suitable desulfurizing agent, such as $HgCl_2$, in a suitable solvent such as DMF or acetonitrile.



XII

Compounds of formula (Ib), where R_1 is an amine may be prepared using a general procedure described by M. Haake and B. Schummfelder (Synthesis, 1991, 753). According to this procedure (Method E, Scheme VII), intermediate XIII bearing two suitable leaving groups Z, such as phenoxy groups, is reacted sequentially with amines R_1 and R_6R_8NH in a suitable solvent such as methanol or isopropanol to provide the desired product. Reaction of the first amine may be carried out at about room temperature and reaction of the second amine is preferentially carried out with heating at the reflux temperature of the solvent. If XIII is allowed to react with a bifunctional nucleophile intermediate XIV, where Y is a nucleophilic heteroatom such as N, O or S, one may obtain the product of formula (Ib) where R_1 and R_6 form a heterocyclic ring. Intermediate XIII may be prepared by reaction of III (R_4 = H) with dichlorodiphenoxymethane, which in turn, may be prepared by heating diphenyl carbonate with PCl_5 (R.L. Webb and C.S. Labow, J. Het. Chem., 1982, 1205).

Scheme VII (Method E)

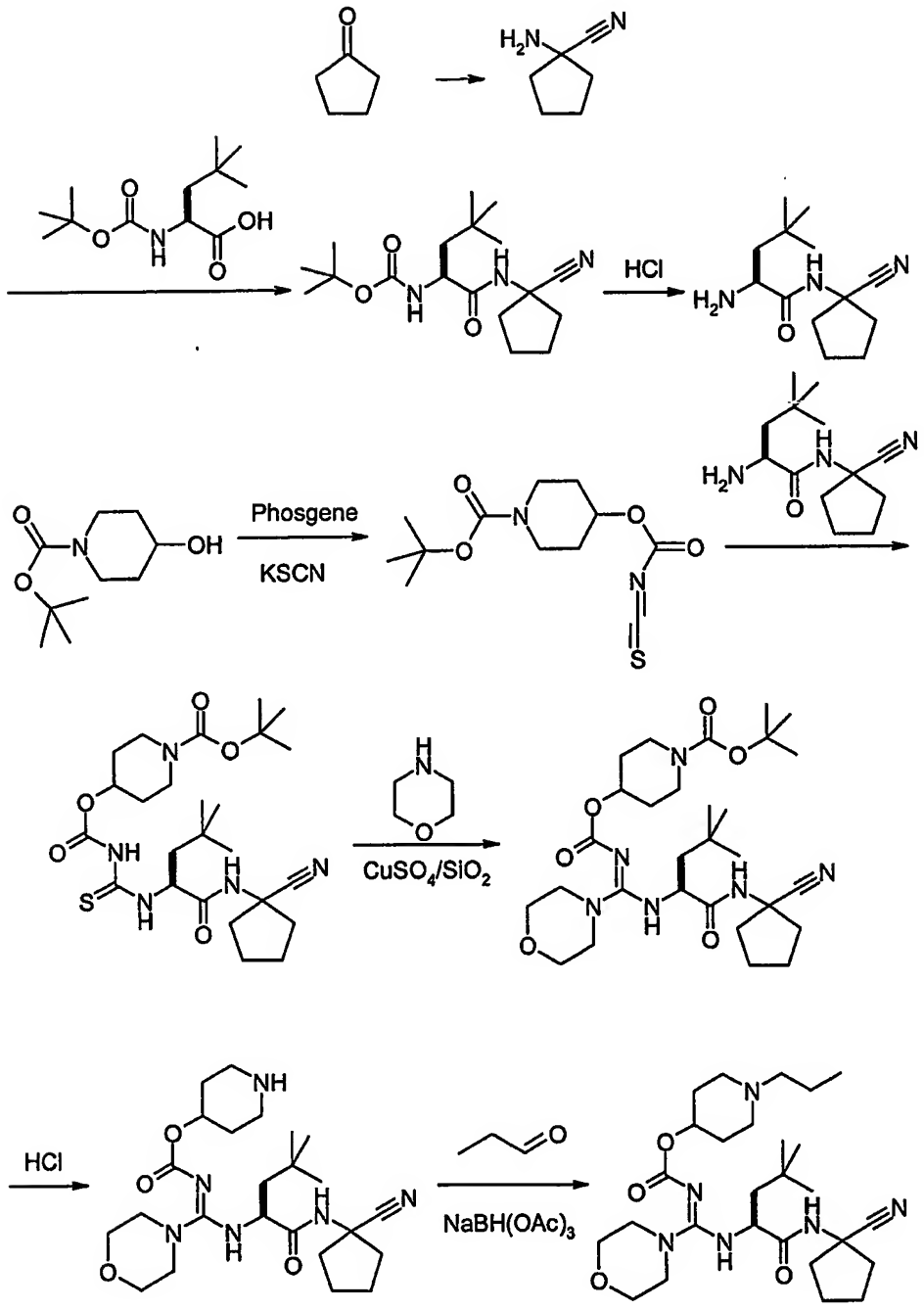


In order that this invention be more fully understood, the following example is set forth. This example is for the purpose of illustrating embodiments of this invention, and is not to be construed as limiting the scope of the invention in any way.

The example which follows is illustrative and, as recognized by one skilled in the art, particular reagents or conditions could be modified as needed for individual compounds. Starting materials used in the scheme below are either commercially available or easily prepared from commercially available materials by those skilled in the art.

EXAMPLE 1

{[1-(1-Cyano-cyclopentylcarbamoyl)-3,3-dimethyl-butylamino]-morpholin-4-yl-methylene}-carbamic acid 1-propyl-piperidin-4-yl ester



A mixture of cyclopentanone (15.6 mL, 0.176 mol), magnesium sulfate (31.9 g, 0.264 mol), sodium cyanide (9.5 g, 0.194 mol) and ammonium chloride (4.7 g, 0.088 mol) in 2.0 M NH_3/CH_3OH (300 mL) was heated at 60 ^oC for 6 h before it was filtered through

silica gel. The filtrate was concentrated and stirred with magnesium sulfate in dichloromethane for 6 h. It was filtered, concentrated and dried in vacuo to give 1-amino-cyclopentanecarbonitrile (17 g, 87.7%).

To a stirred solution of 2-*tert*-butoxycarbonylamino-4,4-dimethyl-pentanoic acid (5 g, 20.3 mmol) and *N*-methyl morpholine (4.46 mL, 40.6 mmol) in THF (40 mL) at 0 °C was added isobutyl chloroformate (2.64 mL, 20.3 mmol) and, after 10 min, the solution of 1-amino-cyclopentanecarbonitrile (3.35 g, 30.5 mmol) in THF (40 mL). The mixture was allowed to warm to room temperature and stirred overnight. It was diluted with water, extracted with dichloromethane, washed with brine, dried (sodium sulfate) and concentrated to give the crude product. Chromatography on silica gel (dichloromethane:MeOH = 30:1) gave [1-(1-cyano-cyclopentylcarbamoyl)-3,3-dimethyl-butyl]-carbamic acid *tert*-butyl ester (6.15 g, 89.6%).

The above ester (6.15 g, 18.2 mmol) was added to 4N HCl in 1,4-dioxane (40 mL) and stirred for 10 min. It was then diluted with ether. Filtration gave 2-amino-4,4-dimethyl-pentanoic acid (1-cyano-cyclopentyl)-amide hydrochloride salt (5.6 g).

To a cold solution of phosgene (1.89 M in toluene, 47.3 mL, 89.4 mmol) was added a solution of *tert*-butyl 4-hydroxy-1-piperidinecarboxylate (15g, 74.5 mmol) in THF (100 mL). The mixture was allowed to warm to room temperature and stirred overnight. The solvent was removed under vacuum and to the residue was added acetonitrile (100 mL) and sodium thiocyanate (7.2 g, 74.5 mmol). This mixture was stirred overnight, the insoluble solid was removed by filtration and the filtrate was used as a stock solution of the isothiocyanatoformate (~ 0.745 mmol/mL).

2-Amino-4,4-dimethyl-pentanoic acid (1-cyano-cyclopentyl)-amide hydrochloride salt (1.38 g, ~ 5.0 mmol) was suspended in 10 mL of THF. Triethylamine (1.42 mL, 10 mL) was added. To the flask was next added the above stock solution of isothiocyanatoformate (34 mL). The resulting mixture was stirred at rt for 3 h. The

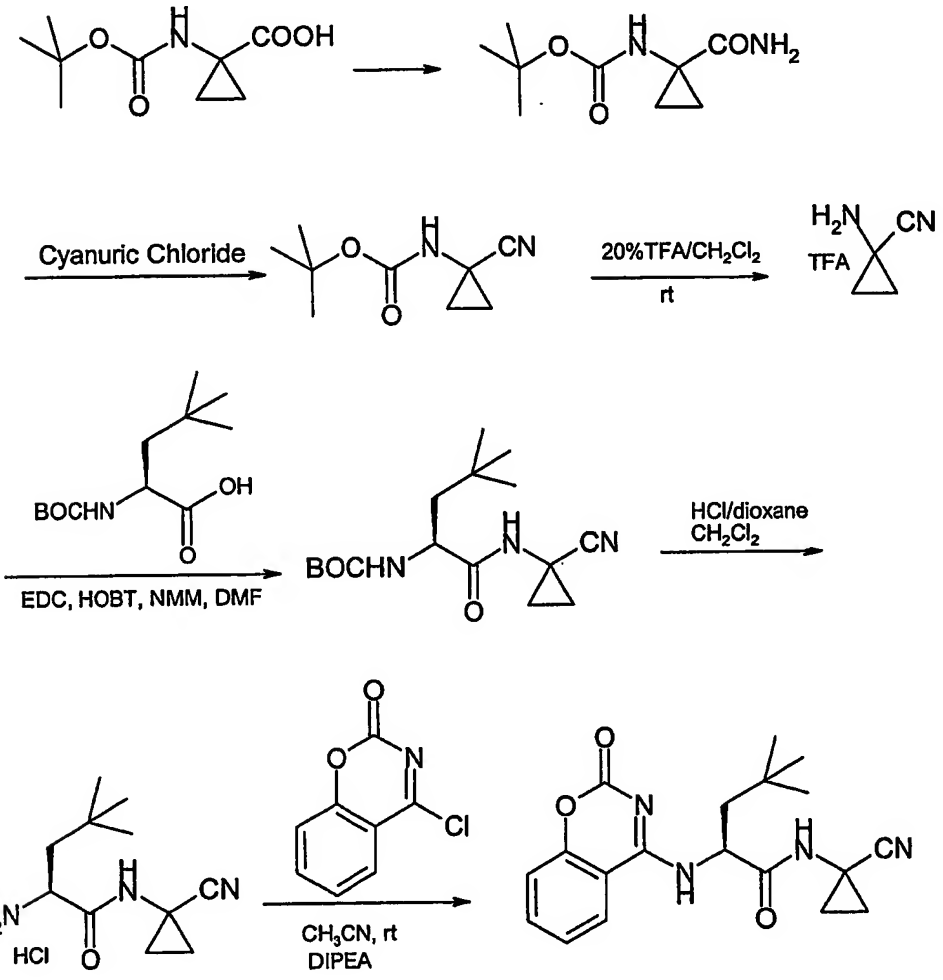
solvent was removed in vacuo. The residue was purified by flash chromatography on silica gel eluting with 10% EtOAc in dichloromethane to give the thiourea (1.02 g, 39%).

The above thiourea (839 mg, 1.6 mmol) and morpholine (0.42 mL, 4.8 mmol) were dissolved in 10 mL of THF. Copper sulfate on silica gel (1.00 g, 2.5 mmol) was added followed by 0.22 mL of triethylamine. This mixture was stirred at 50 ^{o}C for 5 h. After cooling to room temperature, the solid was removed by filtration and washed with acetonitrile. The filtrate was concentrated under reduced pressure and then purified by flash chromatography on silica gel, eluting with a mixture of methylene chloride and MeOH (10:1) to give 4-{[1-(1-cyano-cyclopentylcarbamoyl)-3,3-dimethyl-butylamino]-morpholin-4-yl-methylenecarbamoyloxy}-piperidine-1-carboxylic acid *tert*-butyl ester (653 mg, 70%).

To a stirred solution of the above *tert*-butyl ester (653 mg, 1.13 mmol) in 1,4-dioxane (10 mL) was added HCl (4N in 1,4-dioxane, 10 mL) and the mixture was stirred for 30 min before the solvent was removed under vacuum. The residue was dried in vacuo to give {[1-(1-cyano-cyclopentylcarbamoyl)-3,3-dimethyl-butylamino]-morpholin-4-yl-methylene}-carbamic acid piperidin-4-yl ester hydrochloride salt (738 mg). Then to a mixture of the hydrochloride salt (246 mg, ~ 0.37 mmol) in THF (20 mL) was added propionaldehyde (71 µl, 0.96 mmol) and, 20 min later, sodium triacetoxyborohydride (305 mg, 1.44 mmol). The mixture was stirred for 2 h before it was diluted with water, extracted with dichloromethane, washed with brine, dried (sodium sulfate) and concentrated to give the crude product. Chromatography on silica gel (dichloromethane:methanol = 10:1) gave the title compound (10 mg, 5%).

EXAMPLE 2

Synthesis of (S)-4,4-Dimethyl-2-[2-oxo-2,3-dihydro-benzo[*e*][1,3]oxazin-(4Z)-ylideneamino]-pentanoic acid (1-cyano-cyclopropyl)-amide



To a stirred solution of Boc-1-aminocyclopropane-1-carboxylic acid (25 g, 124 mmol) and triethylamine (19 mL, 1.1 equivalent) in THF (200 mL) at –10 °C ethylchloroformate (13 mL, 1.1 equivalent) was added slowly. The mixture was stirred at this temperature for 20 min before a solution of ammonia in 1,4-dioxane (0.5 M, 300 mL) was added. It was allowed to warm to room temperature and stirred overnight. It was concentrated, diluted with water, extracted with dichloromethane, washed with brine,

dried (sodium sulfate), concentrated again and dried to give (1-carbamoyl-cyclopropyl)-carbamic acid *tert*-butyl ester (18 g, 72.5%)

To a stirred solution of (1-carbamoyl-cyclopropyl)-carbamic acid *tert*-butyl ester (5.7 g, 28.4 mmol) in DMF (50 mL) was added cyanuric chloride (2.6 g, 14.2 mmol) and it was stirred at room temperature for 1 h before it was diluted with water (400 mL). The product precipitated and filtration gave (1-cyano-cyclopropyl)-carbamic acid *tert*-butyl ester (2.79 g, 53.9%)

To (1-cyano-cyclopropyl)-carbamic acid *tert*-butyl ester (1.0 g, 5.5 mmol) in dichloromethane (5 mL) was added 10 mL of 20% trifluoroacetic acid in dichloromethane. The reaction was stirred for 10 min at room temperature and the solvents removed on an evaporator. Hexane was added to the residue and evaporated. The crude deprotected amine was used for the next step. MS = 197 (M+TFA)

To (S)-2-tert-butoxycarbonylamino-4,4-dimethyl-pentanoic acid (1.0 g, 4.08 mmol) in dry DMF (20 mL), at 0 ^{0}C, was added EDC (1.27 g, 6.6 mmol) and HOBT (0.9 g, 6.6 mmol). The reaction was stirred for 30 min at 0 ^{0}C and to this was added the above 1-amino-cyclopropanecarbonitrile-TFA salt (1.0 g, 5.1 mmol) and N-methyl morpholine (1.34 g, 13.26 mmol). The reaction was stirred at 0 ^{0}C for 1 h and at room temperature overnight. Solvent was removed on an evaporator and the residue was extracted with ethyl acetate. The organic fraction was washed with sat. sodium bicarbonate, water, brine and dried over anhydrous sodium sulfate. Solvent was evaporated and the crude product was purified by flash column chromatography using silica gel and ethyl acetate/hexane 1:1 to afford 700 mg (55%) of the desired product.

To the above [(S)-1-(1-cyano-cyclopropylcarbamoyl)-3,3-dimethyl-butyl]-carbamic acid *tert*-butyl ester (0.7 g, 2.26 mmol) in dichloromethane (3 mL) at 0 ^{0}C, was added 4M HCl/dioxane. The reaction was stirred at room temperature for 30 min and the solvent removed. Diethyl ether was added to the residue and the solvent removed on an

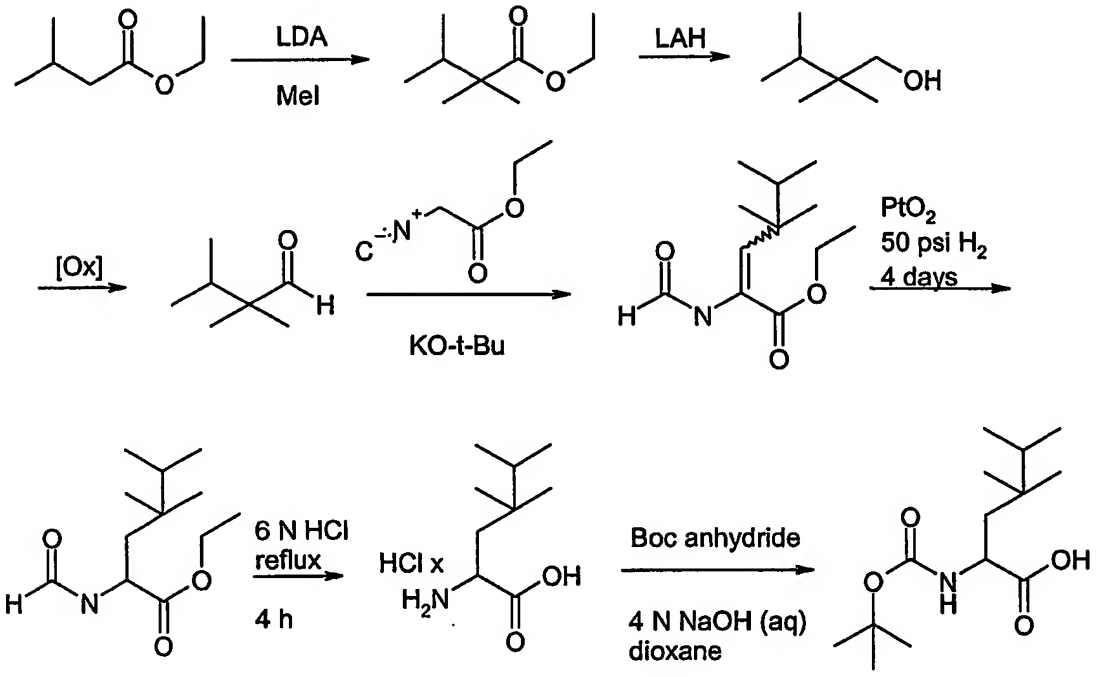
evaporator to afford 550 mg of the deprotected amine. This was used as is for the next step.

To the above (S)-2-amino-4,4-dimethyl-pentanoic acid (1-cyano-cyclopropyl)-amide hydrochloride (0.28 g, 1.14 mmol) in acetonitrile (10 mL) at 0 ^{0}C, was added diisopropyl ethylamine (0.46 mL, 2.26 mmol) and the reaction stirred for 20 min. To this was then added 4-chloro-benzo[*e*][1,3]oxazin-2-one (that was prepared by treating 4a,8a-dihydro-benzo[*e*][1,3]oxazine-2,4-dione with phosphorus pentachloride in phosphorus oxychloride at reflux for 3 h followed by removing solvent) and the reaction was stirred at room temperature overnight. Evaporation of the solvent, extraction with ethyl acetate, followed by washing with saturated sodium bicarbonate and water gave the crude product. This was purified by flash column chromatography on silica gel using ethyl acetate to give 50 mg (12.45%) of the title compound.MS = 355 (M+1) .

The following examples are illustrative of methods used for preparation of unnatural amino acids used as intermediates in the preparation of compounds of the invention by procedures described in the General Synthetic Methods section.

EXAMPLE 3

2-*tert*-Butoxycarbonylamino-4,4,5-trimethyl-hexanoic acid



Lithium diisopropylamide (1.5 M solution in cyclohexane/THF/ethylbenzene) (113 mL, 169 mmol, 1.1 equiv) was syringed into a 1000 mL round-bottom flask under a blanket of Ar. Dry THF (150 mL) was added and the mixture was cooled to -78 °C with a dry-ice/acetone bath. 3-Methyl-butanoic acid ethyl ester (20 g, 23 mL, 154 mmol, 1.0 equiv) was added dropwise from a syringe over a 10 min period followed by stirring at -78 °C for 1 h. Methyl iodide (10.5 mL, 169 mmol, 1.1 equiv) was added dropwise from a syringe over a 10 min period and the creamy mixture was stirred for 1 h at -78 °C, resulting in a very thick mixture. The dry-ice bath was removed and replaced with an ice bath at 0 °C. Another 150 mL of dry THF was added followed by another addition of LDA (113 mL, 169 mmol, 1.1 equiv). The resulting mixture was stirred for 10 min and then the flask was re-immersed in a dry-ice/acetone bath. Stirring was continued for another 50 min and then methyl iodide was added dropwise (10.5 mL, 169 mmol, 1.1 equiv) and the dry-ice/acetone bath was removed and the resulting mixture was stirred at ambient temperature for 14 h. The reaction mixture was quenched with 3 mL of conc. HCl and 2 N HCl was added until the pH was adjusted to <1. The mixture was further diluted with 150 mL water and 500 mL Et_2O. The layers were separated and the organic

layer was washed with 1 x 100 mL 2 N HCl, 1 x 100 mL saturated $NaHCO_3$, and 1 x 200 mL brine. The organic layer was dried over Na_2SO_4 and then concentrated *in vacuo* to provide 2,2,3-trimethylbutanoic acid ethyl ester as an orange oil mixed with ethyl benzene (36.4 g of which 22.1 g was product by NMR). The mixture was used without further purification.

A 500 mL round-bottom flask equipped with a stir bar was flushed with Ar and charged with 50 mL dry THF and a 1 M solution of LAH in Et_2O (87.5 mL, 87.5 mmol, 0.625 equiv). The solution was cooled to 0 °C with an ice bath and the above ethyl ester (22.1 g, 140 mmol, 1.0 equiv) (approximately a 50% solution in ethylbenzene) was added dropwise at such a rate that the solution did not reflux (required 50 min). After addition of the ester, the reaction was stirred at 0 °C for 2 h and then at ambient temperature for 14 h. The reaction solution was re-cooled to 0 °C and carefully quenched by addition of EtOAc. 1 N NaOH was added until a granular precipitate formed (7.5 mL). The mixture was filtered on a pad of diatomaceous earth which was then washed 3 x 100 mL Et_2O. The organics were combined and dried over Na_2SO_4. The solution was decanted and concentrated *in vacuo* to yield 2,2,3-trimethyl-butanol as a nearly colorless oil (11.7 g of alcohol in 15.4 g of a mix with ethylbenzene). The crude product was used without further purification.

A 1000 mL round-bottom-flask was equipped with a stir bar, flushed with Ar and charged with 300 mL dry CH_2Cl_2 and oxalyl chloride (13.2 mL, 151 mmol, 1.5 equiv). The solution was cooled to -78 °C with a dry-ice/acetone bath. Dry DMSO (21.5 mL, 302 mmol, 3.0 equiv) was added dropwise over a 30 min period (vigorous gas evolution). The above alcohol (11.7 g, 100 mmol, 1.0 equiv) was added (with residual ethylbenzene) over a 10 min period. The resulting solution was stirred for 90 min. Triethylamine (56 mL, 403 mmol, 4.0 equiv) was added over 5 min and the cold-bath was removed. The resulting creamy white mixture was stirred at room temperature over 1.5 h. The reaction mixture was carefully diluted with 200 mL water (more gas evolution). Layers were separated and the organic phase was washed with 2 N HCl (1 x 100 mL) and brine (1 x 100 mL). The organic layer was dried over Na_2SO_4, decanted

and concentrated *in vacuo*. The crude aldehyde was fractionally distilled through a 4 inch Vigoreux column at 57-67 °C at 15 mm Hg to provide the 2,2,3-trimethyl-butanal (9.1 g) as a colorless oil.

A clean and dry 250 mL round-bottom flask was equipped with a stir bar and flushed with Ar. Dry THF was added (40 mL) followed by addition of a 1.0 M solution of KO-*t*-Bu (32.2 mL, 32.2 mmol, 1.05 equiv). The solution was cooled to -78 °C in a dry-ice/acetone bath. Ethyl isocyanoacetate (3.35 mL, 30.7 mmol, 1.0 equiv) was added dropwise over a 10 min period. The resulting mixture was stirred an additional 5 min followed by addition, via syringe, of 2,2,3-trimethyl-butanal (3.5 g, 30.7 mmol, 1.0 equiv). The cold-bath was removed and resulting mixture was stirred at room temperature for 1 h. The reaction mixture was diluted by addition of a mix of 125 mL Et_2O, 20 g ice, 2 mL AcOH. After the ice melted, 50 mL of water was added and the layers were mixed and separated. The organic layer was washed with 1 x 50 mL sat. $NaHCO_3$ and dried over Na_2SO_4. The organic layer was decanted and concentrated. The crude enamide was purified by flash chromatography on silica gel using CH_2Cl_2 to 4% MeOH in CH_2Cl_2 to provide 2-formylamino-4,4,5-trimethyl-hex-2-enoic acid ethyl ester as a thick oil (4.54 g); MS: 228 (M+1).

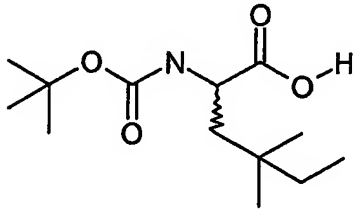
The above ethyl ester (4.54 g, 20 mmol, 1.0 equiv) was dissolved in 35 mL of MeOH in a Parr bottle followed by addition of PtO_2 (1 g, 4.4 mmol, 0.22 equiv). The mixture was shaken on a Parr hydrogenation apparatus for 4 days at which time MS showed consumption of the starting material; MS: 230 (M+1), 216 (M+1 of methyl ester). The liquid was carefully decanted and the Pt was washed three times with 20 mL MeOH followed each time by decantation, being careful not to allow the Pt to dry (if allowed to dry, the Pt may ignite). The MeOH solutions were combined and concentrated to a thick oil that was suspended in 25 mL of 6 N HCl and the mixture was refluxed for 4 h during which time 5 mL of conc. HCl was added at the end of each of the first 3 h.. The mixture was cooled and the water and excess HCl were removed on a rotovap at a bath temperature of 70 °C. After about 50% concentration, a flaky crystalline solid formed. The mixture was cooled to 0 °C and the precipitate was collected by filtration. The

filtrate was again concentrated by about 50% and cooled again to 0 °C to provide a second crop of crystals. The crystals were combined and dried under high vacuum to provide 2-amino-4,4,5-trimethyl-hexanoic acid hydrochloride as an off-white crystalline solid (2.32 g); MS: 174 (M-Cl+1).

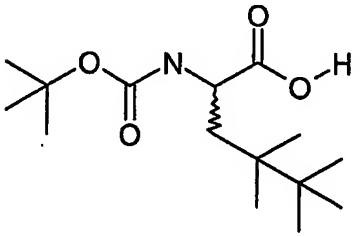
The above amino acid salt (2.32 g, 11.1 mmol, 1.0 equiv) was dissolved in 100 mL of 50/50 dioxane/4 N NaOH. The solution was cooled to 0 °C and Boc anhydride (3.6 g, 16.6 mmol, 1.5 equiv) was added. The cold-bath was removed and the reaction stirred at ambient temperature for 16 h. The pH was carefully adjusted to 2 with conc. HCl, and the product was extracted with 3 x 100 mL CH_2Cl_2. The organic layers were combined and dried over Na_2SO_4. The solution was decanted and concentrated using 100 mL of hexane as a chaser to provide a thick glass, which was triturated with 100 mL of hexane. After vigorous stirring for 4 h, a waxy solid resulted which was filtered and dried in air to provide the title compound (1.42 g); MS: 272 (M-H).

The following Boc-protected amino acids were prepared in a manner identical to this method from the commercially available esters:

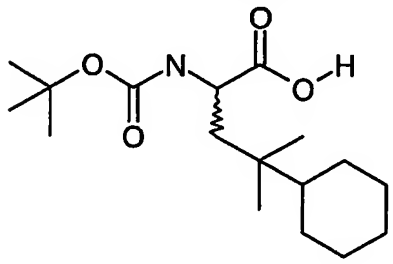
2-*tert*-Butoxycarbonylamino-4,4-dimethyl-hexanoic acid



2-*tert*-Butoxycarbonylamino-4,4,5,5-tetramethyl-hexanoic acid

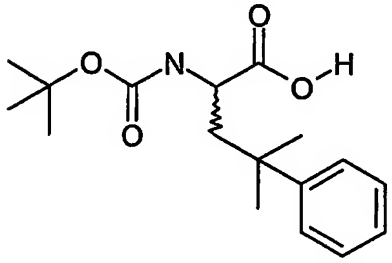


2-*tert*-Butoxycarbonylamino-4-cyclohexyl-4-methyl-pentanoic acid

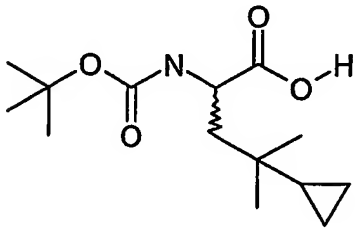


In addition, the following Boc-protected amino acids may be prepared by an appropriate modification of this procedure:

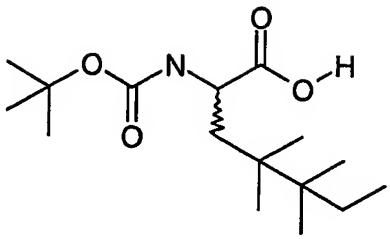
2-*tert*-Butoxycarbonylamino-4-methyl-4-phenyl-pentanoic acid



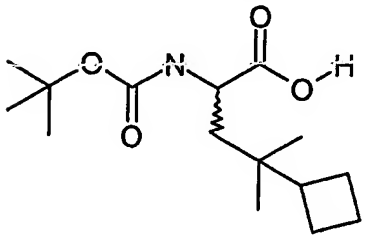
2-*tert*-Butoxycarbonylamino-4-cyclopropyl-4-methyl-pentanoic acid



2-*tert*-Butoxycarbonylamino-4,4,5,5-tetramethyl-heptanoic acid

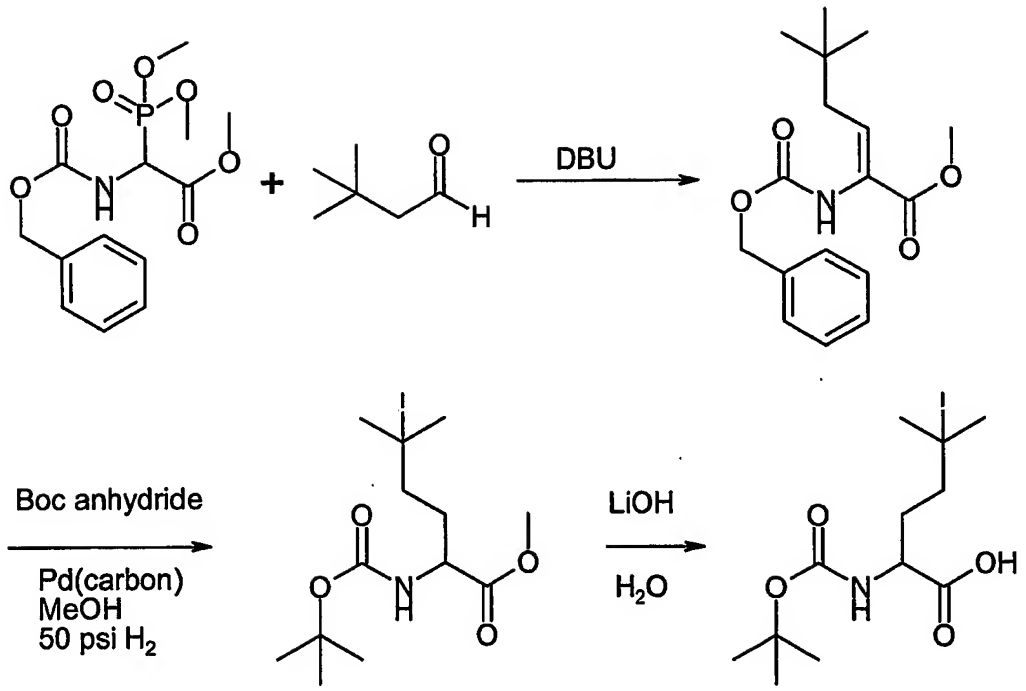


2-*tert*-Butoxycarbonylamino-4-cyclobutyl-4-methyl-pentanoic acid



EXAMPLE 4

2-*tert*-Butoxycarbonylamino-5,5-dimethyl-hexanoic acid

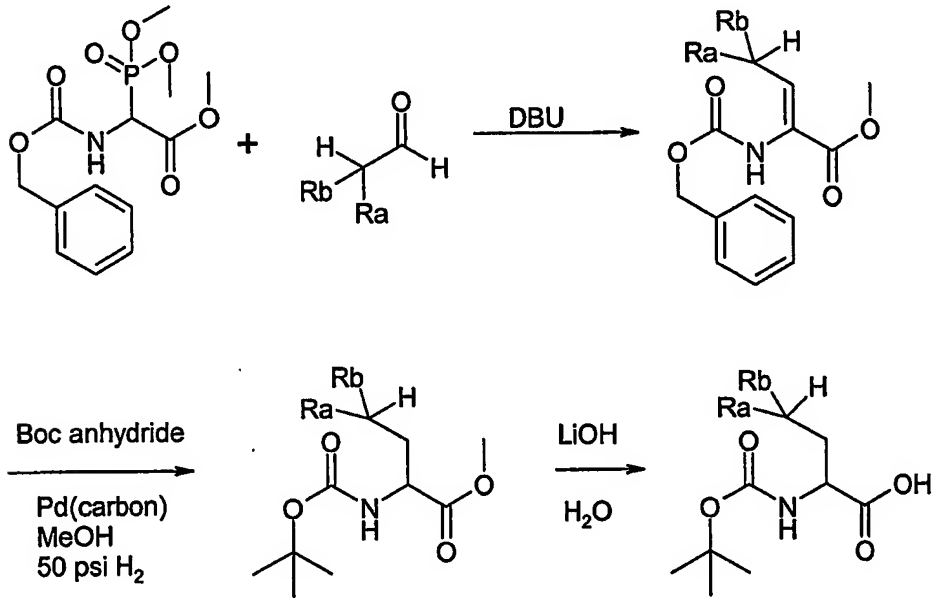


N-(Benzyloxycarbonyl)-α-phosphonoglycine trimethyl ester (2 g, 6.0 mmol, 1.0 equiv) was dissolved in dry THF (20 mL). *tert*-Butylacetaldehyde (0.758 mL, 6.0 mmol, 1.0 equiv) and DBU (0.903 mL, 6.0 mmol, 1.0 equiv) were added and the reaction mixture was stirred for 16 h. The solution was diluted with 100 mL of CH_2Cl_2 and washed with water (1 x 50 mL), and brine (1 x 50 mL). The organic layer was dried over Na_2SO_4, decanted and concentrated *in vacuo* to provide 2-benzyloxycarbonylamino-5,5-dimethyl-hex-2-enoic acid methyl ester as a thick oil (1.73 g, 94%) which was used without further purification; MS: 306 (M+1).

The above ester (1.73 g, 5.67 mmol, 1.0 equiv) was dissolved in a Parr bottle with Boc anhydride (1.36 g, 6.23 mmol, 1.0 equiv) and MeOH (35 mL). Pd on carbon (Degussa type) (0.5 g) was added. The mixture was shaken under 50 psi H_2 for16 h. The mixture was filtered through diatomaceous earth followed by washing of the diatomaceous earth with 3 x 50 mL MeOH. The organics were combined and concentrated to provide 2-*tert*-butoxycarbonylamino-5,5-dimethyl-hexanoic acid methyl ester as a very thick oil which was used without further purification.

The above ester (1.31 g, 4.79 mmol, 1.0 equiv) was dissolved in 50 mL of MeOH. 1 N LiOH (50 mL) was added and the mixture was stirred 16 h. Concentrated HCl was added carefully until the pH approached 2 at which time a bright white solid precipitated. The solid was collected by filtration and washed 2 x 20 mL water and dried under vacuum to provide the title compound (1.05 g, 85%); MS: 258 (M-1).

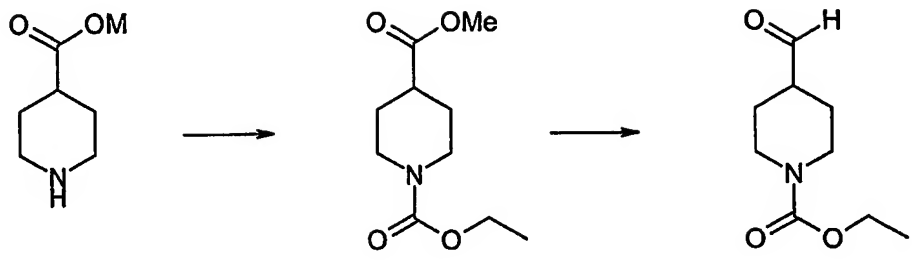
The procedure described in this example may be used with any commercially available aldehyde to prepare the corresponding Boc-protected amino acid as outlined below.



Additionally, many aldehydes may be prepared from the corresponding commercially available esters using the procedure described in Example 5.

EXAMPLE 5

4-Formyl-piperidine-1-carboxylic acid ethyl ester



Methyl isonipecotate (10 g, 69.9 mmol, 1.0 equiv) was dissolved in 50 mL of THF and 250 mL of saturated aqueous bicarbonate. Ethyl cholorformate (9.1 g, 83.9 mmol, 1.2 equiv) was added dropwise and the resulting solution was stirred for 2 h. The reaction mixture was diluted with 250 mL diethyl ether and the layers were separated. The organic layer was washed with brine and dried over Na_2SO_4. The liquid was decanted and concentrated *in vacuo* to yield piperidine-1,4-dicarboxylic acid 1-ethyl ester 4-methyl ester as a pink liquid (12.8 g) which was used without further purification.

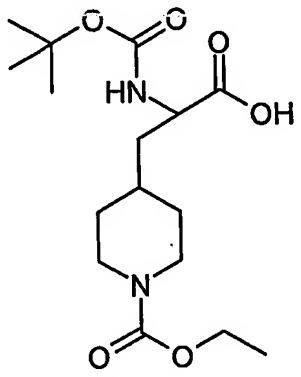
The above ester (12.8 g, 59.5 mmol, 1.0 equiv) was dissolved in 50 mL of dry CH_2Cl_2 under Ar and cooled to –78 °C. A 1 Molar solution of DIBAL-H in CH_2Cl_2 (149 mL, 149 mmol, 2.5 equiv) was added dropwise over a 30 min period. The cold bath was removed and the reaction solution allowed to warm to ambient temperature. At this time EtOAc (10 mL) was added dropwise to quench the excess DIBAL-H. 100 mL of 1H HCl (aq) was added dropwise over a 30 min period with rapid stirring. The resulting mixture was filtered on a pad of diatomaceous earth and the filtrate was dried over Na_2SO_4, decanted and concentrated to yield 4-hydroxymethyl-piperidine-1-carboxylic acid ethyl ester as a nearly colorless oil that was used without further purification.

The above alcohol (7.5 g, 40.0 mmol, 1.0 equiv) was dissolved in 500 mL of CH_2Cl_2. Pyridinium chlorochromate (12.96 g, 60.1 mmol, 1.5 equiv) was added and resulting mixture was stirred for 16 h. The dark liquid was decanted and the solvent was removed *in vacuo*. The residue was triturated with 500 mL of diethyl ether and the mixture was filtered. The filtrate was washed with 150 mL of 1 N HCl and dried over Na_2SO_4. The liquid was decanted and concentrated by rotary evaporation to yield 4-formyl-piperidine-1-carboxylic acid ethyl ester as a light brown oil (6.1 g).

The following example illustrates how this aldehyde may be used in a manner analogous to that described in Example 4.

EXAMPLE 6

4-(2-*tert*-Butoxycarbonylamino-2-carboxy-ethyl)-piperidine-1-carboxylic acid ethyl ester.



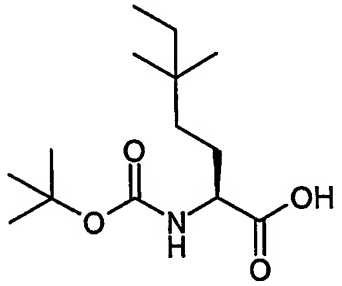
N-(Benzyloxycarbonyl)-α-phosphonoglycine trimethyl ester (1.0 equiv) is dissolved in dry THF. The above aldehyde (1.0 equiv) and DBU (1.0 equiv) are added and the reaction mixture is stirred for 16 h. The solution is diluted with CH_2Cl_2 and washed with water and brine. The organic layer is dried over Na_2SO_4, decanted and concentrated *in vacuo* to provide 4-(benzyloxycarbonylamino-2-carbomethoxy-ethyl)-piperidine-1-carboxylic acid ethyl ester.

The above ester (1.0 equiv) is dissolved in a Parr bottle with Boc anhydride (1.0 equiv) and MeOH. Pd on carbon (Degussa type) (0.1 equiv) is added. The mixture is shaken under 50 psi H_2. The mixture is filtered on diatomaceous earth followed by washing of the diatomaceous earth with MeOH. The organics are combined and concentrated to provide 4-(2-*tert*-Butoxycarbonylamino-2-carbomethoxy-ethyl)-piperidine-1-carboxylic acid ethyl ester.

The above ester (1.0 equiv) is dissolved in a minimum amount of MeOH. 1 N LiOH (3.0 equiv hydroxide) is added and the mixture is stirred. The aqueous layer is washed with diethyl ether and then acidified to pH = 2. The product is extracted with 2 washes of diethyl ether and the organics are combined and concentrated after drying over Na_2SO_4.

EXAMPLE 7

(2S)-2-(*tert*-Butoxyoxycarbonylamino)-5,5-dimethyl-heptanoic acid.



Lithium aluminum hydride (8.0 g, 211 mmol, 1.0 equiv) was placed in a 500 mL round-bottom flask under Ar. Dry THF (200 mL) was added and the mixture was cooled to –78 °C. 3,3-Dimethyl-pent-4-en-oic acid methyl ester (30 g, 211 mmol, 1.0 equiv) was added dropwise over a 30 min period via a syringe. The cold bath was removed and replaced with an ice-water bath at 0 °C. Stirring was continued for 2 h. The excess LAH was quenched by addition of EtOAc dropwise. 1 N NaOH was added dropwise until a granular precipitate formed (approximately 15 mL). The reaction mixture was filtered on a pad of diatomaceous earth. The filtrate was dried over $MgSO_4$, filtered and concentrated by rotary evaporation to yield 3,3-dimethyl-pent-4-en-ol as a colorless oil (20.2 g, 85 %) which was used without further purification.

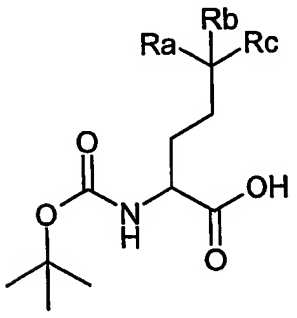
3,3-Dimethyl-pent-4-en-ol (20.2 g, 177 mmol, 1.0 equiv) was dissolved in 500 mL of CH_2Cl_2. Solid pyridinium chlorochromate (57.2 g, 266 mmol, 1.5 equiv) was added and the resulting mixture was stirred 16 h. The liquid was decanted into a 1000 mL RBF and the black tar was washed with CH_2Cl_2 (2 x 100 mL). The combined liquids were concentrated on the rotovap at a bath temperature <20 °C (the aldehyde is quite volatile). The resulting paste was triturated with 500 mL of hexane and the mixture filtered on a

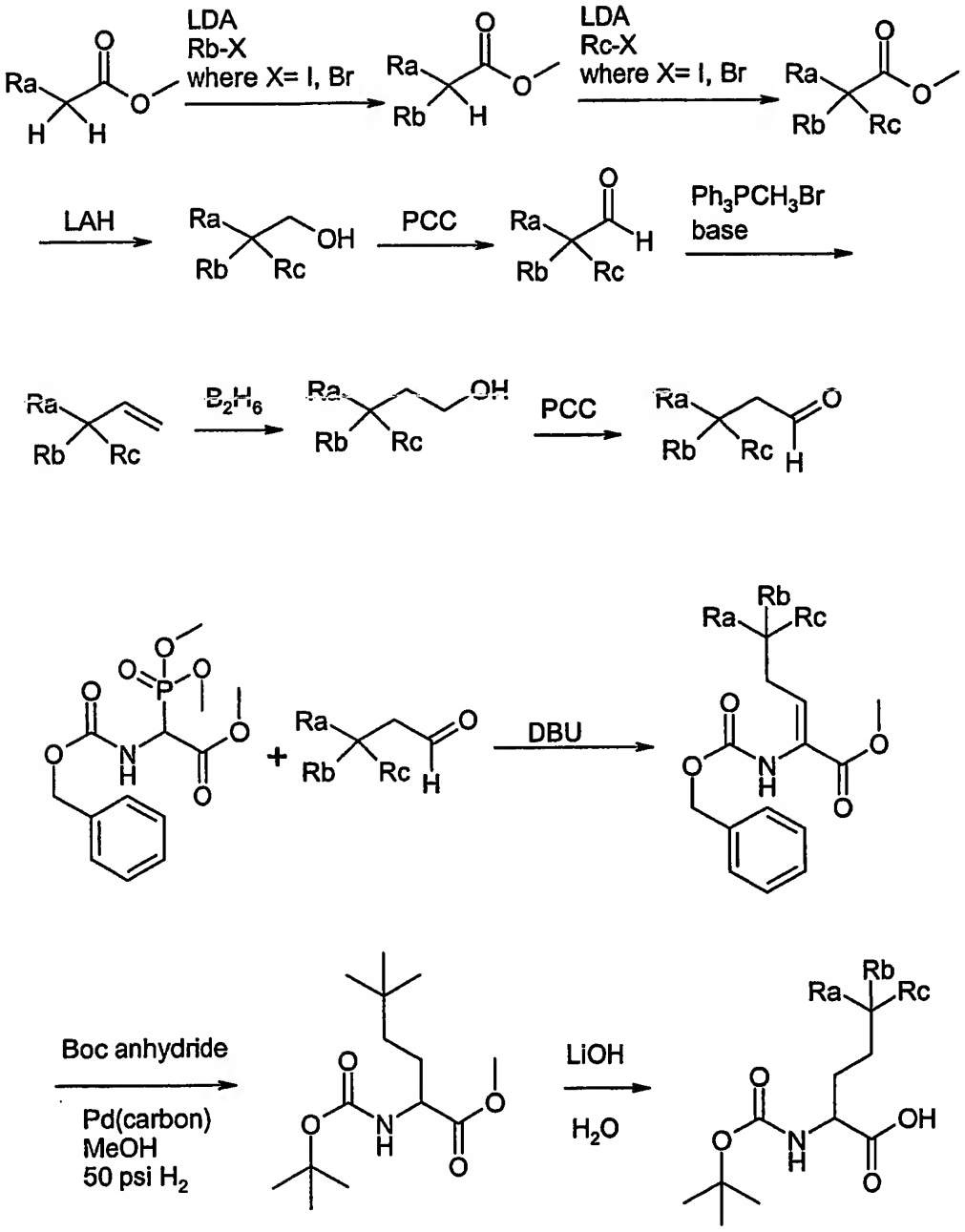
frit. The filtrate was diluted with 150 mL Et_2O, washed with 200 mL of 1 N aqueous HCl, dried over Na_2SO_4, decanted and concentrated to yield 3,3-dimethyl-pent-4-en-al as a light beige liquid (11.6 g, 56 %) that was used without further purification.

N-(Benzyloxycarbonyl)-α-phosphonoglycine trimethyl ester (34.3 g, 103 mmol, 1.0 equiv) was dissolved in dry THF (250 mL) and the solution was cooled to 0 °C. 3,3-Dimethyl-pent-4-en-al (11.6 g, 103 mmol, 1.0 equiv) and DBU (15.5 mL, 103 mmol, 1.0 equiv) were added and the reaction mixture was stirred for 16 h. The solution was diluted with 500 mL of CH_2Cl_2 and washed with 1 x 150 mL water, and 1 x 150 mL brine. The organic layer was dried over Na_2SO_4, decanted and concentrated *in vacuo* to provide 2-benzyloxycarbonylamino-5,5-dimethyl-hept-2,6-dienoic acid methyl ester as a thick oil (31 g, 95% crude). The enamide is purified by flash chromatography on silica using hexanes/EtOAc as mobile phase to yield 2-benzyloxycarbonylamino-5,5-dimethyl-hept-2,6-dienoic acid methyl ester as a thick oil that solidifies on standing.

The above ester may be converted to the title compound by catalytic reduction followed by hydrolysis as described in Example 4.

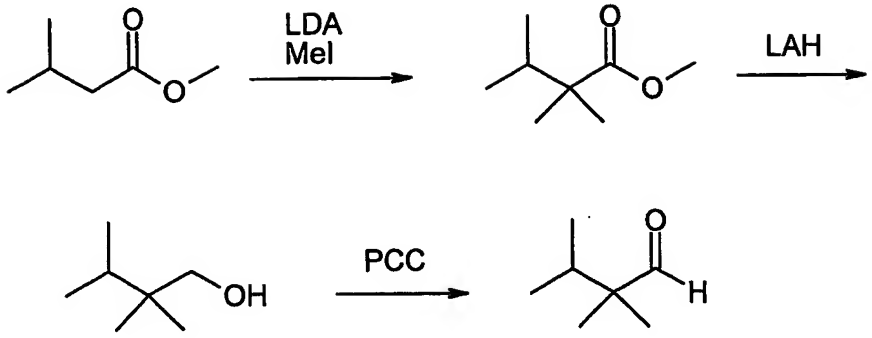
Additionally, Boc-protected amino acids of the formula below may be prepared as outlined for in the following scheme:





EXAMPLE 8

2,2,3-Trimethyl-butanal



Lithium diisopropylamide (1.5 M solution in cyclohexane/THF/ethylbenzene) (113 mL, 169 mmol, 1.1 equiv) was syringed into a 1000 mL round-bottom flask under a blanket of Ar. Dry THF (150 mL) was added and the mixture was cooled to -78 °C with a dry-ice/acetone bath. 3-Methyl-butanoic acid ethyl ester (20 g, 23 mL, 154 mmol, 1.0 equiv) was added dropwise from a syringe over a 10 min period followed by stirring at -78 °C for 1 h. Methyl iodide (10.5 mL, 169 mmol, 1.1 equiv) was added dropwise from a syringe over a 10 min period and the creamy mixture was stirred for 1 h at -78 °C, resulting in a very thick mixture. The dry-ice bath was removed and replaced with an ice bath at 0 °C. Another 150 mL of dry THF was added followed by another addition of LDA (113 mL, 169 mmol, 1.1 equiv). The resulting mixture was stirred for 10 min and then the flask was re-immersed in a dry-ice/acetone bath. Stirring was continued for another 50 min and then methyl iodide was added dropwise (10.5 mL, 169 mmol, 1.1 equiv) and the dry-ice/acetone bath was removed and the resulting mixture was stirred at ambient temperature for 14 h. The reaction mixture was quenched with 3 mL of conc. HCl and 2 N HCl was added until the pH was adjusted to <1. The mixture was further diluted with 150 mL water and 500 mL Et_2O. The layers were separated and the organic layer was washed with 2 N HCl (1 x 100 mL), saturated $NaHCO_3$ (1 x 100 mL), and brine (1 x 200 mL). The organic layer was dried over Na_2SO_4 and then concentrated in vacuo to provide 2,2,3-trimethylbutanoic acid ethyl ester as an orange oil mixed with ethyl benzene (36.4 g of which 22.1 g was product by NMR). The mixture was used without further purification.

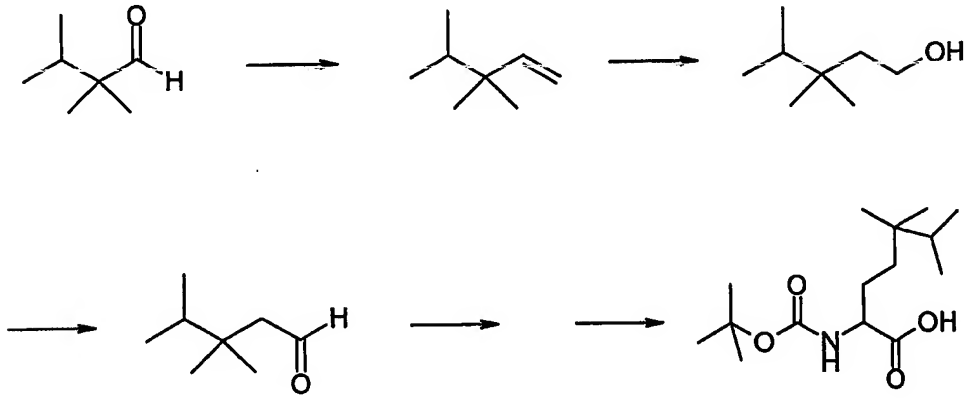
A 500 mL round-bottom-flask equipped with a stir bar was flushed with Ar and charged with 50 mL dry THF and a 1 M solution of LAH in Et_2O (87.5 mL, 87.5 mmol, 0.625 equiv). The solution was cooled to 0 °C with an ice bath and the above ethyl ester (22.1 g, 140 mmol, 1.0 equiv) (approximately a 50% solution in ethylbenzene) was added dropwise at such a rate that the solution did not reflux (required 50 min). After addition of the ester, the reaction was stirred at 0 °C for 2 h and then at ambient temperature for 14 h. The reaction solution was re-cooled to 0 °C and carefully quenched by addition of EtOAc. 1 N NaOH was added until a granular precipitate formed (7.5 mL). The mixture was filtered on a pad of diatomaceous earth which was then washed 3 x 100 mL Et_2O. The organics were combined and dried over Na_2SO_4. The solution was decanted and concentrated in vacuo to yield 2,2,3-trimethyl-butanol as a nearly colorless oil (11.7 g of alcohol in 15.4 g of a mix with ethylbenzene). The crude product was used without further purification.

A 1000 mL round-bottom-flask was equipped with a stir bar, flushed with Ar and charged with 300 mL dry CH_2Cl_2 and oxalyl chloride (13.2 mL, 151 mmol, 1.5 equiv). The solution was cooled to -78 °C with a dry-ice/acetone bath. Dry DMSO (21.5 mL, 302 mmol, 3.0 equiv) was added dropwise over a 30 min period (vigorous gas evolution). The above alcohol (11.7 g, 100 mmol, 1.0 equiv) was added (with residual ethylbenzene) over a 10 min period. The resulting solution was stirred for 90 min. Triethylamine (56 mL, 403 mmol, 4.0 equiv) was added over 5 min and the cold-bath was removed. The resulting creamy white mixture was stirred at room temperature over 1.5 h. The reaction mixture was carefully diluted with 200 mL water (more gas evolution). Layers were separated and the organic phase was washed with 1 x 100 mL 2 N HCl and 1 x 100 mL brine. The organic layer was dried over Na_2SO_4, decanted and concentrated *in vacuo*. The crude aldehyde was distilled fractionally through a 4 inch Vigoreux column at 57-67 °C at 15 mm Hg to provide the 2,2,3-trimethyl-butanal (9.1 g) as a colorless oil.

EXAMPLE 9

2-Benzyloxycarbonylamino-5,5,6-trimethyl-heptanoic acid

The title compound may be prepared from 2,2,3-trimethyl-butanal by the following procedure



Methyltriphenylphosphonium bromide (1.0 equiv) is dissolved under Ar in dry THF. The solution is cooled to –78 °C at which time n-BuLi in hexanes (1.05 equiv) is added dropwise. 2,2,3-Trimethyl-butanal (1.0 equiv) is added dropwise to the stirred solution and the cold bath is removed and the reaction mixture is allowed to warm to ambient temperature. The reaction mixture is quenched by addition of saturated ammonium chloride solution. The mixture is diluted with ether and water and the layers are separated. The organic is dried over Na_2SO_4, decanted and the solution is fractionally distilled through a vigoreux column to give 3,3,4-trimethylpentene.

3,3,4-Trimethylpentene (1 equiv) is dissolved in dry THF under Ar. The reaction mixture is cooled to –78 °C at which time a 1 M solution of borane/dimethylsulfide complex in THF (0.4 equiv) is added dropwise. The cold bath is removed and the reaction mixture is allowed to warm to ambient temperature. The reaction mixture is carefully diluted with a solution of sodium acetate in aqueous hydrogen peroxide (large exess). The reaction mixture is stirred at ambient temperature and then diluted with diethyl ether and the

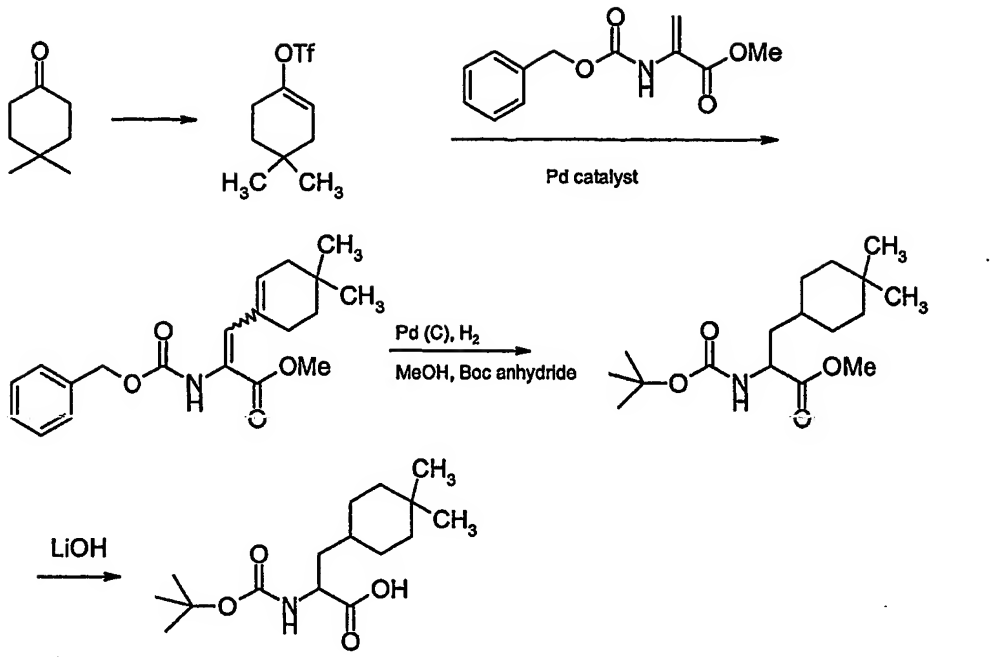
layers are separated. The organic layer is dried over Na_2SO_4, decanted and concentrated. The crude material is purified by fractional distillation to yield 3,3,4-trimethylpentanol.

3,3,4-Trimethylpentanol (1 equiv) is dissolved in CH_2Cl_2. Pyridinium chlorochromate (1.5 equiv) is added and the resulting mixture is stirred at ambient temperature. The liquid is decanted and concentrated by rotary evaporation. The residue is triturated with 1 to 1 diethyl ether/hexane and mixture is filtered and the filtrate is washed with 1 N HCl. The organic layer is dried over Na_2SO_4, decanted and concentrated. The aldehyde is purified by fractional distillation to yield 3,3,4-trimethylpentanal.

This aldehyde may be converted to the title compound by reaction with *N*-(Benzyloxycarbonyl)-α-phosphonoglycine trimethyl ester, followed by catalytic reduction and hydrolysis by the procedures described in Example 4.

EXAMPLE 10

Preparation of 2-*tert*-Butoxycarbonylamino-3-(4,4-dimethyl-cyclohexyl)-propionic acid.



To a solution of 4,4-dimethyl cyclohexanone (4.60 g, 36.5 mmol) in dry THF (82 mL) cooled in a dry ice/acetone bath, was added sodium bis (trimethylsilyl)amide (38 mL of a 1.0 M solution in THF, 38 mmol). The reaction mixture was stirred under an argon atmosphere at –78 °C for 30 min. A solution of 2-(N,N-bis trifluoromethanesulfonyl)amino-5-chloropyridine (15 g, 37.7 mmol) in dry THF (20 mL) was introduced via syringe and the resulting solution was warmed to room temperature and stirred overnight. The reaction mixture was washed with half saturated brine (60 mL) and the aqueous phase was extracted with diethyl ether. The combined organic extracts were dried ($MgSO_4$) and concentrated to provide a dark brown oil (23 g). Chromatography over silica gel using petroleum ether as the eluant provided trifluoro-methane sulfonic acid 4,4-dimethyl-cyclohex-1-enyl ester as a colorless liquid (5.2 g, 56%).

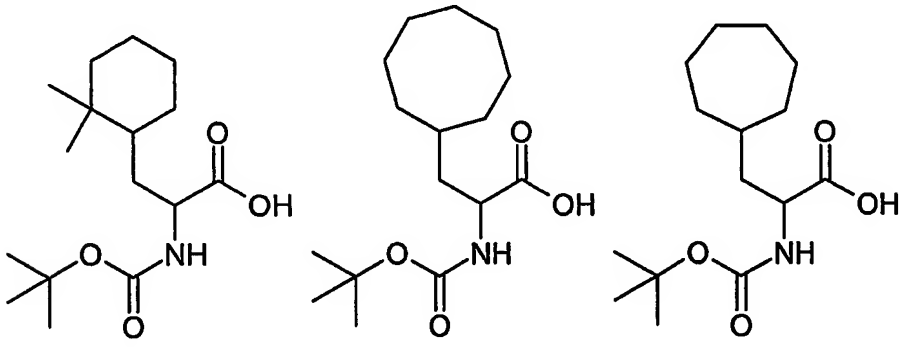
A mixture of the above triflate ester (2.26 g, 8.75 mmol), Cbz dehydroalanine methyl ester (2.10 g, 8.93 mmol), Pd $(OAc)_2$ (160 mg, 0.71 mmol), and KOAc (3.42 g, 34.8 mmol) in dry DMF was stirred at room temperature for 24 h. The reaction mixture was diluted with water (400 mL) and extracted with EtOAc (2 x 150 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. Chromatography of the resulting

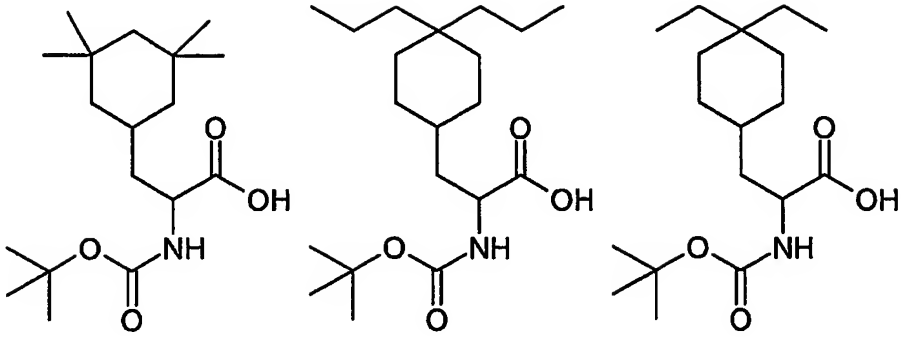
residue over silica gel using 1:20 EtOAc/ hexanes then 3:17 EtOAc/ hexanes provided 2-benzyloxycarbonylamino-3-(4,4-dimethyl-cyclohex-1-enyl)-acrylic acid methyl ester as a yellow oil (1.38 g, 46%).

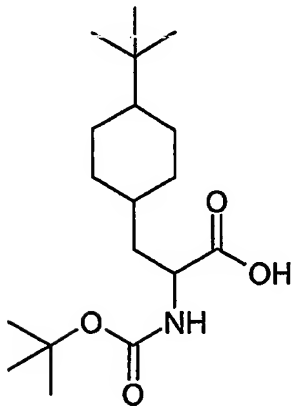
A suspension of the above acrylic acid ester (2.18 g, 6.35 mmol), Boc anhydride (1.52 g, 6.96 mmol), and 10% Pd/ C (300 mg) in MeOH was shaken on a Parr apparatus under 40 psi of hydrogen gas for 17 h. The reaction mixture was filtered through a pad of diatomaceous earth and concentrated to provide 2-tert-butoxycarbonylamino-3-(4,4-dimethyl-cyclohexyl)-propionic acid methyl ester as a yellow oil (1.87 g, 94%).

A suspension of the above methyl ester (1.87 g, 5.97 mmol) and lithium hydroxide monohydrate (1.76 g, 41.9 mmol) in THF (18 mL), MeOH (6 mL), and water (6 mL) was stirred at room temperature for 4 h. The reaction mixture was acidified with 10% citric acid (aqueous) and extracted with diethyl ether (3 x 100 mL). The combined organic layers were dried ($MgSO_4$) and concentrated to provide a the corresponding carboxylic acid as a white foam (1.21 g, 68%).

The following Boc-protected amino acids were prepared using the above procedure starting from the commercially available ketones:

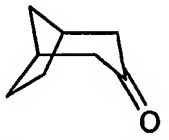




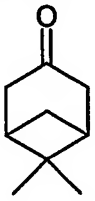


Additionally, the following cyclic ketones may be synthesized according to methods described in the literature and converted by the above procedure, into Boc-protected amino acids:

Sauers, R. R.; Tucker, R. J.; *J Org Chem*, 1963, 28, 876.



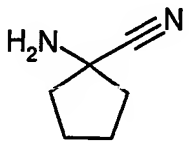
Burgstahler, A. W.; Sticker, R. E.; *Tetrahedron,* 1968, 2435.



The following examples illustrate procedures that may be used to prepare amino nitrile intermediates that may be used to prepare compounds of the invention.

EXAMPLE 11

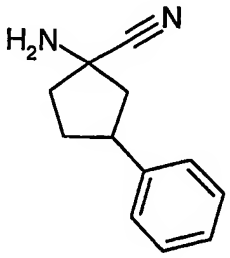
1-Amino-1-cyano-cyclopentane



Cyclopentanone (1 equiv), NaCN (1.1 equiv) and NH_4Cl (1.1 equiv) are mixed together in 2 Molar NH_3/MeOH (4 equiv NH_3). The flask is fitted with a reflux condenser and the mixture is refluxed. At the end of each of the first 3 h an additional equivalent of NH_3 in MeOH is added. The reaction mixture is cooled and the excess solids are filtered away on a frit. The filtrate is concentrated by rotary evaporation and the residue is triturated with diethyl ether and the mixture is filtered again. The filtrate is concentrated on a rotovap. The product is purified, if necessary, by flash chromatography on silica with EtOAc/hexanes as an eluent to yield the titled compound.

EXAMPLE 12

1-Amino-1-cyano-3-phenyl-cyclopentane

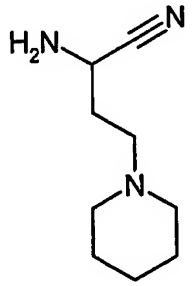


Cyclopent-2-enone (1 equiv) is dissolved in dry THF under Ar. CuI (1.5 equiv) is added and the mixture is cooled to –78 °C. A 1 Molar solution of PhMgBr (1 equiv) is added dropwise. The resulting mixture is slowly warmed to ambient temperature over a 4 h period. The reaction is quenched by the addition of saturated ammonium chloride solution (aq). The product is extracted with diethyl ether. The organic layer is dried over Na_2SO_4, decanted and concentrated. The product ketone is purified by flash chromatography on silica using EtOAc and hexanes as mobile phase.

The above ketone (1 equiv), NaCN (1.1 equiv) and NH_4Cl (1.1 equiv) are mixed together in 2 Molar NH_3/MeOH (4 equiv NH_3). The flask is fitted with a reflux condenser and the mixture is refluxed. At the end of each of the first 3 h an additional equivalent of NH_3 in MeOH is added. The reaction mixture is cooled and the excess solids are filtered away on a frit. The filtrate is concentrated by rotary evaporation and the residue is triturated with diethyl ether and the mixture is filtered again. The filtrate is concentrated on a rotovap. The product is purified, if necessary, by flash chromatography on silica with EtOAc/hexanes as an eluent to yield the titled compound.

EXAMPLE 13

1-Amino-1-cyano-3-(piperid-1-yl)-propane.



Acrolyl chloride (1 equiv) is dissolved in dry methylene chloride and the solution is cooled to –20 °C in a methanol/ice bath. Solid N,O-dimethylhydroxylamine hydrochloride (1 equiv) is added followed by dropwise addition of Et_3N (2.2 equiv). The reaction is stirred and then poured into ice-water. The mixture is diluted with methylene

chloride and the layers separated. The organic layer is dried over Na_2SO_4, decanted and concentrated to yield N-methoxy-N-methyl-propenamide.

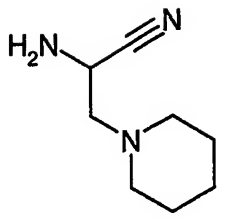
The above amide (1 equiv) is dissolved in THF. Piperidine (1.1 equiv) is added and the reaction solution is stirred at ambient temperature for 48 h. The reaction mixture is concentrated and the product is purified by flash chromatography on silica using $MeOH/CH_2Cl_2$ as mobile phase to yield N-methoxy-N-methyl-3-(piperid-1-yl)-propanamide.

The above amide (1 equiv) is dissolved in dry THF and the solution is cooled to –78 °C. Solid LAH (0.5 equiv) is carefully added. The reaction mixture is then immersed in an ice-bath at 0 °C and stirred 30 min. The reaction is quenched by the addition of EtOAc followed by water. The mixture is diluted with Et_2O and the layers are separated. The organic is washed with brine, dried over Na_2SO_4, decanted and concentrated to yield 3-(piperid-1-yl)-propanal which is used immediately in the next step.

The above aldehyde (1 equiv) is mixed with NaCN (1.1 equiv), NH_4Cl (1.1 equiv) are mixed together in 2 Molar NH_3/MeOH (4 equiv NH_3). The flask is fitted with a reflux condenser and the mixture is refluxed. At the end of each of the first 3 h an additional equivalent of NH_3 in MeOH is added. The reaction mixture is cooled and the excess solids are filtered away on a frit. The filtrate is concentrated by rotary evaporation and the residue is triturated with diethyl ether and the mixture is filtered again. The filtrate is concentrated on a rotovap. The product is purified, if necessary, by flash chromatography on silica with EtOAc/hexanes as an eluent to yield 1-amino-1-cyano-3-(piperid-1-yl)-propane.

EXAMPLE 14

Amino-1-cyano-2-(piperid-1-yl)-ethane.



Bromoacetylchloride (1.0 equiv) is dissolved in dry methylene chloride and the solution is cooled to –20 °C in a methanol/ice bath. Solid N,O-dimethylhydroxylamine hydrochloride (1 equiv) is added followed by dropwise addition of Et_3N (2.2 equiv). The reaction is stirred for 1 h and then poured into ice-water. The mixture is diluted with methylene chloride and the layers separated. The organic layer is dried over Na_2SO_4, decanted and concentrated to yield N-methoxy-N-methyl-2-bromo-ethanamide.

The above amide (1 equiv) is dissolved in THF. Piperidine (1.1 equiv) is added and the reaction solution is stirred at ambient temperature for 48 h. The reaction mixture is concentrated and the product is purified by flash chromatography on silica using $MeOH/CH_2Cl_2$ as the mobile phase to yield N-methoxy-N-methyl-2-(piperid-1-yl)-ethanamide.

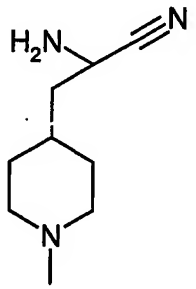
The above amide (1 equiv) is dissolved in dry THF and the solution is cooled to –78 °C. Solid LAH (0.5 equiv) is carefully added. The reaction mixture is then immersed in an ice-bath at 0 °C and stirred 30 min. The reaction is quenched by the addition of EtOAc followed by water. The mixture is diluted with Et_2O and the layers are separated. The organic is washed with brine, dried over Na_2SO_4, decanted and concentrated to yield 3-(piperid-1-yl)-ethanal which is used immediately in the next step.

The above aldehyde (1 equiv) is mixed with NaCN (1.1 equiv) and NH_4Cl (1.1 equiv) in 2 Molar NH_3/MeOH (4 equiv NH_3). The flask is fitted with a reflux condenser and mixture is refluxed for 4 h. At the end of each of the first 3 h an additional equivalent of NH_3 in MeOH is added. The reaction mixture is cooled and the excess solids are filtered away on a frit. The filtrate is concentrated by rotary evaporation and the residue is triturated with diethyl ether and the mixture is filtered again. The filtrate is concentrated

on a rotovap. The product is purified, if necessary, by flash chromatography on silica gel with EtOAc/hexanes as eluent to yield 1-amino-1-cyano-2-(piperid-1-yl)-ethane.

EXAMPLE 15

1-Amino-1-cyano-2-(1-methyl-piperid-4-yl)-ethane.



2-(1-Methyl-piperid-4-yl)-ethanoic acid ethyl ester is prepared from 1-methyl-piperid-4-one (1 equiv), triethyl phosphono acetate (1 equiv) and NaH (1.1 equiv) in benzene followed by reduction of the alkene bond according to the procedure of Cignarella etc. (*J Heterocyclic Chem* 1993, 30 (5), 1337-1340).

The above ester (1 equiv) is dissolved in MeOH and 1 N LiOH (3 equiv of hydroxide) is added. The mixture is stirred until the starting material is consumed. Concentrated HCl is added until the pH = 2 (as judged by pH paper). The mixture is then concentrated by lyophilization to yield 2-(1-methyl-piperid-yl)-ethanoic acid hydrochloride as a mix with LiCl.

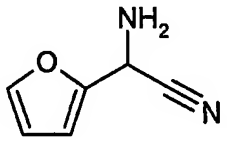
The above mixture (about 1 equiv of carboxylic acid) is suspended in DMF. EDC (1.1 equiv) is added followed by N-methylmorpholine (3.0 equiv). After 20 min, solid N,O-dimethylhydroxylamine hydrochloride is added and the resulting mixture is stirred for 16 h. The mixture is diluted with saturated aqueous bicarbonate solution and the product extracted twice with EtOAc. The organic layer is washed with brine, dried over Na_2SO_4, decanted and concentrated. The product is purified by flash chromatography on silica using MeOH/CH_2Cl_2 as eluent to yield N,O-dimethyl-2-(1-methyl-piperid-4-yl)-ethanamide.

The above amide (1 equiv) is dissolved in dry THF and the solution is cooled to –78 °C. Solid LAH (0.5 equiv) is carefully added. The reaction mixture is then immersed in an ice-bath at 0 °C and stirred. The reaction is quenched by the addition of EtOAc followed by water. The mixture is diluted with Et_2O and the layers are separated. The organic layer is washed with brine, dried over Na_2SO_4, decanted and concentrated to yield 2-(1-methyl-piperid-4-yl)-ethanal which is used immediately in the next step.

The above aldehyde (1 equiv) is mixed with NaCN (1.1 equiv) and NH_4Cl (1.1 equiv) in 2 Molar NH_3/MeOH (4 equiv NH_3). The flask is fitted with a reflux condenser and the mixture is refluxed. At the end of each of the first 3 h an additional equivalent of NH_3 in MeOH is added. The reaction mixture is cooled and the excess solids are filtered away on a frit. The filtrate is concentrated by rotary evaporation and the residue is triturated with diethyl ether and the mixture is filtered again. The filtrate is concentrated on a rotovap. The product is purified, if necessary, by flash chromatography on silica with EtOAc/hexanes as an eluent to yield 1-amino-1-cyano-2-(1-methyl-piperid-4-yl)-ethane.

EXAMPLE 16

Amino-cyano-(furan-2-yl)-methane.



Furfural (1.0 equiv) is mixed with NaCN (1.1 equiv) and NH_4Cl (1.1 equiv) in 2 Molar NH_3/MeOH (4 equiv NH_3). The flask is fitted with a reflux condenser and mixture is refluxed. At the end of each of the first 3 h an additional equivalent of NH_3 in MeOH is added. The reaction mixture is cooled and the excess solids are filtered away on a frit. The filtrate is concentrated by rotary evaporation and the residue is triturated with diethyl ether and the mixture is filtered again. The filtrate is concentrated on a rotovap. The product is purified, if necessary, by flash chromatography on silica gel with EtOAc/hexanes as an eluent to yield amino-cyano-(furan-2-yl)methane.

In addition, the following amino-nitriles may be prepared from the commercially available aldehydes in a manner identical to that for amino-cyano-(furan-2-yl)-methane.

Amino-cyano-(furan-3-yl)-methane
Amino-cyano-(thiophen-2-yl)-methane
Amino-cyano-(thiophen-3-yl)-methane
Amino-cyano-(thiazol-2-yl)-methane
Amino-cyano-(thiazol-4-yl)-methane
Amino-cyano-(thiazol-5-yl)-methane
Amino-cyano-(oxazol-2-yl)-methane
Amino-cyano-(oxazol-4-yl)-methane
Amino-cyano-(oxazol-5-yl)-methane
Amino-cyano-(pyrid-2-yl)-methane
Amino-cyano-(pyrid-3-yl)-methane
Amino-cyano-(pyrid-4-yl)-methane

METHODS OF THERAPEUTIC USE

The compounds of the invention are useful in inhibiting the activity of cathepsin S, K, F, L and B. In doing so, these compounds are useful in blocking disease processes mediated by these cysteine proteases.

Compounds of this invention effectively block degradation of the invariant chain to CLIP by cathepsin S, and thus inhibit antigen presentation and antigen-specific immune responses. Control of antigen specific immune responses is an attractive means for treating autoimmune diseases and other undesirable T-cell mediated immune responses.

Thus, there is provided methods of treatment using the compounds of this invention for such conditions. These encompass autoimmune diseases and other diseases involving inappropriate antigen specific immune responses including, but not limited to, rheumatoid arthritis, systemic lupus erythematosus, Crohn's disease, ulcerative colitis, multiple sclerosis, Guillain-Barre syndrome, psoriasis, Grave's disease, myasthenia gravis, scleroderma, glomerulonephritis, dermatitis including contact and atopic dermatitis, insulin-dependent diabetes mellitus, endometriosis and asthma including allergic asthma. The compounds of the invention can also be used to treat other disorders associated with extracellular proteolysis such as Alzheimer's disease and atherosclerosis. The compounds of the invention can also be used to treat other disorders associated with inappropriate autoimmune responses, T-cell mediated immune responses, or extracellular proteolysis mediated by cathepsin S, unrelated to those listed above or discussed in the Background of the Invention. Therefore, the invention also provides methods of modulating an autoimmune disease comprising administering to a patient in need of such treatment a pharmaceutically effect amount of a compound according to the invention.

Compounds of the invention also inhibit cathepsin K. In doing so, they may block inappropriate degradation of bone collagen and other bone matrix proteases. Thus, there is provided a method for treating diseases where these processes play a role such as osteoporosis. Inhibition of cathepsins F, L, and B are also within the scope of the invention due to similarity of the active sites in cysteine proteases as described above.

For therapeutic use, the compounds of the invention may be administered in any conventional dosage form in any conventional manner. Routes of administration include, but are not limited to, intravenously, intramuscularly, subcutaneously, intrasynovially, by infusion, sublingually, transdermally, orally, topically or by inhalation. The preferred modes of administration are oral and intravenous.

The compounds of this invention may be administered alone or in combination with adjuvants that enhance stability of the inhibitors, facilitate administration of pharmaceutical compositions containing them in certain embodiments, provide increased

dissolution or dispersion, increase inhibitory activity, provide adjunct therapy, and the like, including other active ingredients. Advantageously, such combination therapies utilize lower dosages of the conventional therapeutics, thus avoiding possible toxicity and adverse side effects incurred when those agents are used as monotherapies. Compounds of the invention may be physically combined with the conventional therapeutics or other adjuvants into a single pharmaceutical composition. Advantageously, the compounds may then be administered together in a single dosage form. In some embodiments, the pharmaceutical compositions comprising such combinations of compounds contain at least about 15%, but more preferably at least about 20%, of a compound of the invention (w/w) or a combination thereof. Alternatively, the compounds may be administered separately (either serially or in parallel). Separate dosing allows for greater flexibility in the dosing regime.

As mentioned above, dosage forms of the compounds of this invention include pharmaceutically acceptable carriers and adjuvants known to those of ordinary skill in the art. These carriers and adjuvants include, for example, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, buffer substances, water, salts or electrolytes and cellulose-based substances. Preferred dosage forms include, tablet, capsule, caplet, liquid, solution, suspension, emulsion, lozenges, syrup, reconstitutable powder, granule, suppository and transdermal patch. Methods for preparing such dosage forms are known (see, for example, H.C. Ansel and N.G. Popovish, *Pharmaceutical Dosage Forms and Drug Delivery Systems*, 5th ed., Lea and Febiger (1990)). Dosage levels and requirements are well-recognized in the art and may be selected by those of ordinary skill in the art from available methods and techniques suitable for a particular patient. In some embodiments, dosage levels range from about 10-1000 mg/dose for a 70 kg patient. Although one dose per day may be sufficient, up to 5 doses per day may be given. For oral doses, up to 2000 mg/day may be required. As the skilled artisan will appreciate, lower or higher doses may be required depending on particular factors. For instance, specific dosage and treatment regimens will depend on factors such as the patient's general health profile, the severity and course of the patient's disorder or disposition thereto, and the judgment of the treating physician.

ASSESSMENT OF BIOLOGICAL PROPERTIES

Expression and Purification of recombinant human Cathepsin S

Cloning of human cathepsin S:
U937 RNA was subjected to reverse transcriptase / polymerase chain reaction with primer A (5'cacaatgaaacggctggtttg 3') and primer B (5'ctagatttctgggtaagaggg 3') designed to specifically amplify the cathepsin S cDNA. The resulting 900 bp DNA fragment was subcloned into pGEM-T (Promega) and sequenced to confirm its identity. This construct was used for all subsequent manipulations. This procedure is typical for cloning of known genes and is established in its field.

Human Pre-Pro-Cat S was removed from pGem-T vector (Promega, 2800 Woods Hollow Rd, Madison, WI 53711) by digestion with restriction enzyme SacII, followed by treatment with T4 DNA polymerase to generate a blunt end, and a second restriction enzyme digest with SalI. It was subcloned into pFastBac1 donor plasmid (GibcoBRL, 8717 Grovemont Cr., Gaithersburg, MD 20884) which had been cut with restriction enzyme BamH1 and blunt-ended and then cut with restriction enzyme SalI. The ligation mixture was used to transform DH5a competent cells (GibcoBRL) and plated on LB plates containing 100ug/mL ampicillin. Colonies were grown in overnight cultures of LB media containing 50ug/mL Ampicillin, plasmid DNA isolated and correct insert confirmed by restriction enzyme digestion. Recombinant pFastBac donor plasmid was transformed into DH10Bac competent cells (GibcoBRL). Large white colonies were picked from LB plates containing 50ug/mL kanamycin, 7ug/mL gentamicin, 10ug/mL tetracycline, 100ug/mL Bluo-gal, and 40ug/mL IPTG. DNA was isolated and used to transfect Sf9 insect cells using CellFECTIN reagent (GibcoBRL). Cells and supernatant were harvested after 72 hours. Viral supernatant was passaged twice and presence of Cat S confirmed by PCR of the supernatant.

SF9 cells were infected with recombinant baculovirus at a MOI of 5 for 48-72 hrs. Cell pellet was lysed and incubated in buffer at pH 4.5 at 37 for 2 hours to activate Cat S from pro-form to active mature form (Bromme, D & McGrath, M., Protein Science, 1996, 5:789-791.) Presence of Cat S was confirmed by SDS-PAGE and Western blot using rabbit anti-human proCat S.

Inhibition of Cathepsin S

Human recombinant cathepsin S expressed in Baculovirus is used at a final concentration of 10 nM in buffer. Buffer is 50 mM Na acetate, pH 6.5, 2.5 mM EDTA, 2.5 mM TCEP. Enzyme is incubated with either compound or DMSO for 10 min at 37 ^{0}C. Substrate 7-amino-4-methylcoumarin, CBZ-L-valyl-L-valyl-L-arginineamide (custom synthesis by Molecular Probes) is diluted to 20 uM in water (final concentration of 5 M), added to assay and incubated for additional 10 minutes at 37 ^{0}C. Compound activity is measured by diminished fluorescence compared to DMSO control when read at 360 nm excitation and 460 nm emission.

Examples listed above were evaluated for inhibition of cathepsin S in the above assay. All had IC_{50} values of 100 micromolar or below.

Inhibition of Cathepsin K, F, L and B:

Inhibition of these enzymes by particular compounds of the invention may be determined without undue experimentation by using art recognized methods as provided hereinbelow each of which is incorporated herein by reference:

Cathepsin B, and L assays are to be found in the following references:

1. Methods in Enzymology, Vol.244, Proteolytic Enzymes: Serine and Cysteine Peptidases, Alan J. Barrett, ed.

Cathepsin K assay is to be found in the following reference:

2. Bromme, D., Okamoto, K., Wang, B. B., and Biroc, S. (1996) *J. Biol. Chem.* **271**, 2126-2132.

Cathepsin F assays are to be found in the following references:

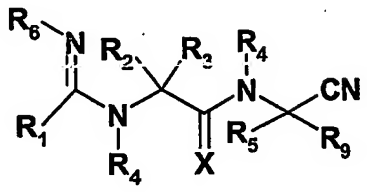
3. Wang, B., Shi, G.P., Yao, P.M., Li, Z., Chapman, H.A., and Bromme, D. (1998) *J. Biol. Chem.* **273**, 32000-32008.

4. Santamaria, I., Velasco, G., Pendas, A.M., Paz, A., and Lopez-Otin, C (1999) J. *Biol. Chem.* **274**, 13800-13809.

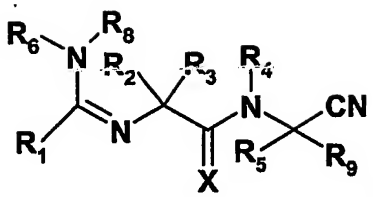
Preferred compounds to be evaluated for inhibition of Cathepsin K, F, L and B in the above assays desirably have IC_{50} values of 100 micromolar or below.

What is claimed is:

1. A compound of the formula (Ia) or (Ib):



(Ia),



(Ib)

wherein:

R_1 is a bond, hydrogen, C1-10 alkyl, C1-10 alkoxy, aryloxy, C3-8 cycloalkyl, C3-8 cycloalkyloxy, aryl, benzyl, tetrahydronaphthyl, indenyl, indanyl, C1-10alkylsulfonylC1-10alkyl, C3-8cycloalkylsulfonylC1-10alkyl, arylsulfonylC1-10alkyl, heterocyclyl selected from azepanyl, azocanyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, indolinyl, pyranyl, tetrahydropyranyl, tetrahydrothiopyranyl, thiopyranyl, furanyl, tetrahydrofuranyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, tetrazolyl, pyrazolyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, benzoxazolyl, benzisoxazolyl, quinolinyl, tetrahydroquinolinyl, isoquinolinyl, tetrahydroisoquinolinyl, quinazolinyl, tetrahydroquinazolinyl and quinoxalinyl, heterocyclyloxy wherein the heterocyclyl moiety is selected from those herein described in this paragraph, hydroxy or amino; wherein R_1 is optionally substituted by one or more R_a;

R_a is a bond, C1-10 alkyl, C3-8 cycloalkyl, aryl, tetrahydronaphthyl, indenyl, indanyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, indolinyl, furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, triazolyl,

tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, benzoxazolyl, benzisoxazolyl, quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, C1-10 alkoxy, C1-10alkanoyl, C1-10alkanoyloxy, aryloxy, benzyloxy, C1-10 alkoxycarbonyl, aryloxycarbonyl, aroyloxy, carbamoyl wherein the nitrogen atom may be independently mono or di-substituted by C1-10 alkyl, aryl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, indolinyl, furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl, isoquinolinyl, quinazolinyl or quinoxalinyl,

or R_a is C1-10 alkanoylamino, aroylamino, C1-10 alkylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, arylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, ureido wherein either nitrogen atom may be independently substituted by C1-10 alkyl, aryl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, indolinyl, furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl, isoquinolinyl, quinazolinyl or quinoxalinyl,

or R_a is C1-10 alkoxycarbonylamino, aryloxycarbonylamino, C1-10 alkylcarbamoyloxy, arylcarbamoyloxy, C1-10 alkylsulfonylamino, arylsulfonylamino, C1-10 alkylaminosulfonyl, arylaminosulfonyl, amino wherein the nitrogen atom may be independently mono or di-substituted by C1-10 alkyl, aryl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, indolinyl, furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl, isoquinolinyl, quinazolinyl or quinoxalinyl,

or R_a is halogen, hydroxy, oxo, carboxy, cyano, nitro, carboxamide, amidino or guanidino, R_a may be further optionally substituted by one or more R_b;

with the proviso that R_1 and R_a simultaneously cannot be a bond;

R_b is a C1-6 saturated or unsaturated branched or unbranched carbon chain optionally partially or fully halogenated wherein one or more carbon atoms are optionally replaced by O, N, S(O), $S(O)_2$ or S and wherein said chain is optionally independently substituted with 1-2 oxo groups, $-NH_2$, or one or more C1-4 alkyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, indolinyl, furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl, isoquinolinyl, quinazolinyl or quinoxalinyl;

or R_b is C3-6 cycloalkyl, aryl, aryloxy, benzyloxy, halogen, hydroxy, oxo, carboxy, cyano, nitro, mono-C1-5alkylamino, di-C1-5alkylamino, carboxamide, amidino or guanidino;

R_2 is hydrogen or C1-3 alkyl;

R_3 is a bond, hydrogen, alkyl wherein one or more carbon atoms are optionally replaced by O, S or N wherein it shall be understood if N is not substituted by R_c then it is NH, or R_3 is C2-10alkylene, heterocyclylC1-5 alkyl wherein the heterocyclic moiety is selected from pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, 8-aza-bicyclo[3.2.1]octane, silinane, piperazinyl, indolinyl, furanyl, tetrahydrofuranyl, pyranyl, tetrahydropyranyl, tetrahydrothiopyranyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, dihydrobenzofuranyl, octohydrobenzofuranyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, tetrahydroquinolinyl, quinolinyl, tetrahydroisoquinolinyl, isoquinolinyl, quinazolinyl and quinoxalinyl, C3-8 cycloalkyl, arylC1-5alkyl or aryl wherein R_3 is optionally substituted by one or more R_c;

R_c is C3-8 cycloalkyl, aryl, indanyl, indenyl, bicyclo[2.2.1]heptanyl, bicyclo[2.2.2]octanyl, bicyclo[4.1.0]heptanyl, bicyclo[3.1.0]hexanyl, bicyclo[1.1.1]pentanyl, spiroC8-12 cycloalkyl, cubanyl, 1,2,3,4-

tetrahydronaphthyl, decahydronaphthyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, indolinyl, furanyl, tetrahydrofuranyl, pyranyl, tetrahydropyranyl, tetrahydrothiopyranyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, dihydrobenzofuranyl, octohydrobenzofuranyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, tetrahydroquinolinyl, quinolinyl, tetrahydroisoquinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, aryloxy, aroyl, aryloxycarbonyl, aroyloxy,

or R_c is aroylamino, alkylthio, arylthio, aryloxycarbonylamino, arylcarbamoyloxy, arylsulfonylamino, arylaminosulfonyl, amino wherein the nitrogen atom may be independently mono or di-substituted by C1-10 alkyl, aryl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, indolinyl, furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl, isoquinolinyl, quinazolinyl or quinoxalinyl,

or R_c is halogen, hydroxy, oxo, carboxy, cyano, nitro, amidino or guanidino, R_c may be further optionally substituted by one or more R_d;

R_d is C1-5 alkyl, C3-6 cycloalkyl, aryl, arylC1-5alkyl, C1-5 alkoxy, aryloxy, arylC1-5alkoxy, aroyl, amino, halogen, hydroxy, oxo, carboxy, cyano, nitro, amidino or guanidino;

R_2 and R_3 together with the carbon they are attached optionally form a nonaromatic 5-7 membered cycloalkyl or heterocyclic ring;

each R_4 is independently hydrogen, hydroxy or C1-3 alkyl;

R_5 is hydrogen, alkyl, alkoxy, alkoxyalkyl or arylalkyl;

R_9 is hydrogen, alkyl wherein one or more carbon atoms are optionally replaced by O, S or N wherein it shall be understood if N is not substituted by R_e then it is NH, or R_9 is

cycloalkyl, aryl, heterocyclyl, aryl, heteroaryl or cyano, wherein R_9 is optionally substituted by one or more R_e;

R_e is selected from alkyl, cycloalkyl, aryl, aroyl, heterocyclyl, heteroaryl, halogen, hydroxy, oxo, carboxy, cyano, nitro, amidino and guanidino, R_e may be further optionally substituted by one or more R_f;

R_f is selected from alkyl, cycloalkyl, aryl optionally substituted by one or more groups selected from halogen, methyl or methoxy, heterocyclyl, heteroaryl, alkoxy, aryloxy, aroyl, arylalkoxy, alkoxycarbonyl, aryloxycarbonyl, alkanoyloxy, aroyloxy, carbamoyl wherein the nitrogen atom may be independently mono or di-substituted by alkyl, aryl, heterocyclyl or heteroaryl, alkanoylamino, aroylamino, alkylcarbamoyl, arylcarbamoyl, alkylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, arylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, ureido wherein either nitrogen atom may be independently substituted by alkyl, aryl, heterocyclyl or heteroaryl, alkoxycarbonylamino, aryloxycarbonylamino, alkylcarbamoyloxy, arylcarbamoyloxy, alkylsulfonylamino, arylsulfonylamino, alkylaminosulfonyl, arylaminosulfonyl, amino wherein the nitrogen atom may be independently mono or di-substituted by alkyl, aryl, heterocyclyl or heteroaryl, halogen, hydroxy, oxo, carboxy, cyano, nitro, amidino and guanidino;

or R_5 and R_9 together with the carbon they are attached form a 3 to 7-membered monocyclic carbocycle or a 7 to 14-membered bicyclic carbocycle optionally bridged, wherein either carbocycle is optionally benzofused and optionally substituted with one or more R_g;

R_g is selected from alkyl, aryl, alkoxycarbonyl, aryloxycarbonyl, arylalkoxycarbonyl, carbamoyl wherein the nitrogen atom may be optionally

mono or di-substituted with a group selected from alkyl, cycloalkyl, aryl, arylalkyl, heterocyclyl, heteroaryl, halogen, hydroxy, carboxy and cyano;

R_6 is

hydrogen, hydroxy, nitrile or

a C1-6 saturated or unsaturated branched or unbranched alkyl optionally partially or fully halogenated wherein one or more C atoms are optionally replaced by O, NH, S(O), $S(O)_2$ or S and wherein said chain is optionally independently substituted with 1-2 oxo groups, -NH_2, one or more C1-4 alkyl, C3-7 cycloalkyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, indolinyl, pyranyl, thiopyranyl, furanyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl, isoquinolinyl, quinazolinyl, benzoxazolyl or quinoxalinyl;

wherein R_1 and R_6 in the formulas (Ia) or (Ib) optionally form a 4 to 8 membered mono- or 7-14 membered polycyclo heteroring system, each aromatic or nonaromatic, wherein each ring is optionally substituted by one or more R_7;

each R_7 and R_8 are independently:

hydrogen, C1-5 alkyl chain optionally interrupted by one or two N, O or $S(O)_m$ and optionally substituted by 1-2 oxo, amino, hydroxy, halogen, C1-4alkyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, indolinyl, pyranyl, thiopyranyl, furanyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl, isoquinolinyl, quinazolinyl, benzoxazolyl or quinoxalinyl,

aryl, aryloxy, aroyl, furanyl, thienyl, pyrrolyl, imidazolyl, pyridinyl, pyrimidinyl, C1-5 alkanoyl, C1-5 alkoxycarbonyl, aryloxycarbonyl, benzyloxycarbonyl,

C1-5 alkanoylamino, aroylamino, C1-5 alkylthio, arylthio C1-5 alkylsulfonylamino, arylsulfonylamino, C1-5 alkylaminosulfonyl, arylaminosulfonyl, C3-6 cycloalkyl and benzyloxy

each of the aforementioned are optionally halogenated,

halogen, hydroxy, oxo, carboxy, nitrile, nitro or $NH_2C(O)$-;

m is 0, 1 or 2;

and

X is =O, =S or =N-R_6 wherein R_6 is as defined above, or the

pharmaceutically acceptable salts, esters, tautomers, individual isomers and mixtures of isomers thereof.

2. The compound according claim 1 wherein:

R_1 and R_6 of the formula (Ia) or formula (Ib) form:

a monocyclic 5, 6 or 7 membered aromatic or nonaromatic heterocyclic ring optionally substituted by R_7;

a bicyclic ring having one 5, 6 or 7 membered aromatic or nonaromatic heterocyclic ring fused to a second 5-7 membered aromatic or nonaromatic heterocyclic or carbocyclic ring wherein each ring is optionally independently substituted by one or more R_7;

or a tricyclic ring wherein the abovementioned bicyclic ring is further fused to a third 5-7 membered aromatic or nonaromatic heterocyclic or carbocyclic ring wherein each ring is optionally independently substituted by one or more R_7;

R_2 is hydrogen or methyl or ethyl;

R_3 is a bond, hydrogen, C1-10 alkyl wherein one or more carbon atoms are optionally replaced by O, S or N, or R_3 is C2-5alkylene, C3-7 cycloalkyl, heterocyclylC1-5 alkyl wherein the heterocyclic moiety is selected from pyrrolidinyl, piperidinyl, morpholinyl,

thiomorpholinyl, 8-aza-bicyclo[3.2.1]octane, silinane, piperazinyl, indolinyl, furanyl, tetrahydrofuranyl, pyranyl, tetrahydropyranyl, tetrahydrothiopyranyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, pyridinyl, pyrimidinyl, pyrazinyl and indolyl, arylC1-3alkyl or aryl wherein R_3 is optionally substituted by one or more R_c;

R_c is C3-7 cycloalkyl, aryl, indanyl, indenyl, bicyclo[2.2.1]heptanyl, bicyclo[2.2.2]octanyl, bicyclo[4.1.0]heptanyl, bicyclo[3.1.0]hexanyl, bicyclo[1.1.1]pentanyl, spiroC8-10 cycloalkyl, cubanyl, 1,2,3,4-tetrahydronaphthyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, indolinyl, furanyl, tetrahydrofuranyl, pyranyl, tetrahydropyranyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, aryloxy, aroyl, aryloxycarbonyl, aroyloxy,
or R_c is aroylamino, arylthio, aryloxycarbonylamino, arylcarbamoyloxy, arylsulfonylamino, arylaminosulfonyl, amino wherein the nitrogen atom may be independently mono or di-substituted by C1-5 alkyl, aryl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, indolinyl, furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl, isoquinolinyl, quinazolinyl or quinoxalinyl,
or R_c is halogen, hydroxy, oxo, carboxy, cyano, nitro, amidino or guanidino, R_c may be further optionally substituted by one or more R_d;

R_d is C1-5 alkyl, C3-6 cycloalkyl, aryl, arylC1-4 alkyl, C1-5 alkoxy, aryloxy, arylC1-5alkoxy, aroyl, halogen, hydroxy, oxo or cyano;

R_4 is hydrogen or methyl;

R_9 is hydrogen, C1-12 alkyl wherein one or more carbon atoms are optionally replaced by O, S or N, C3-7 cycloalkyl, heterocyclyl selected from pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl and indolinyl, heteroaryl selected from furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, tetrazolyl, thiadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, indolyl, isoindolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, purinyl, quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, carbazolyl, phenothiazinyl and phenoxazinyl, aryl or cyano, wherein R_9 is optionally substituted by one or more R_e;

R_e is selected from C1-8 alkyl, C3-7 cycloalkyl, aryl, aroyl, heterocyclyl selected from pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl and indolinyl; heteroaryl selected from furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, tetrazolyl, thiadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, indolyl, isoindolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, purinyl, quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, carbazolyl, phenothiazinyl and phenoxazinyl, halogen, hydroxy, oxo, carboxy, cyano, nitro, amidino and guanidino, R_e may be further optionally substituted by one or more R_f;

R_f is selected from C1-8 alkyl, C3-7 cycloalkyl, aryl optionally substituted by one or more groups selected from halogen, methyl or methoxy, heterocyclyl selected from pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl and indolinyl; heteroaryl selected from furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, tetrazolyl, thiadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, indolyl, isoindolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, purinyl, quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, carbazolyl, phenothiazinyl and phenoxazinyl, C1-8 alkoxy, aryloxy, aroyl, arylC1-8alkoxy, C1-8 alkoxycarbonyl, aryloxycarbonyl, C1-8 alkanoyloxy,

aroyloxy, carbamoyl wherein the nitrogen atom may be independently mono or di-substituted by C1-8 alkyl, aryl, heterocyclyl selected from pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl and indolinyl, or heteroaryl selected from furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, tetrazolyl, thiadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, indolyl, isoindolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, purinyl, quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, carbazolyl, phenothiazinyl and phenoxazinyl, C1-8 alkanoylamino, aroylamino, C1-8 alkylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, arylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, ureido wherein either nitrogen atom may be independently substituted by alkyl, aryl, heterocyclyl selected from pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl and indolinyl, or heteroaryl selected from furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, tetrazolyl, thiadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, indolyl, isoindolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, purinyl, quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, carbazolyl, phenothiazinyl and phenoxazinyl, alkoxycarbonylamino, aryloxycarbonylamino, alkylcarbamoyloxy, arylcarbamoyloxy, alkylsulfonylamino, arylsulfonylamino, alkylaminosulfonyl, arylaminosulfonyl, amino wherein the nitrogen atom may be independently mono or di-substituted by alkyl, aryl, heterocyclyl selected from pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl and indolinyl, or heteroaryl selected from furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, tetrazolyl, thiadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, indolyl, isoindolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, purinyl, quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, carbazolyl, phenothiazinyl and

phenoxazinyl, halogen, hydroxy, oxo, carboxy, cyano, nitro, amidino and guanidino;

or R_5 and R_9 together with the carbon they are attached form a 3 to 7-membered monocyclic carbocycle or a 7 to 14-membered bicyclic carbocycle optionally bridged, wherein either carbocycle is optionally benzofused and optionally substituted with one or more R_g;

R_g is selected from C1-8 alkyl, aryl, C1-8 alkoxycarbonyl, aryloxycarbonyl, arylC1-8alkoxycarbonyl, carbamoyl wherein the nitrogen atom may be optionally mono or di-substituted with a group selected from C1-8 alkyl, C3-7 cycloalkyl, aryl, arylC1-8alkyl, heterocyclyl selected from pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl and indolinyl, or heteroaryl selected from furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, tetrazolyl, thiadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, indolyl, isoindolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, purinyl, quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, carbazolyl, phenothiazinyl and phenoxazinyl, halogen, hydroxy, carboxy and cyano;

R_7 and R_8 are independently hydrogen, C1-5 alkyl, C3-6 cycloalkyl, aryl, C1-5 alkoxy, aryloxy, benzyloxy each of the aforementioned are optionally halogenated, halogen, hydroxy, oxo, carboxy, nitrile, nitro or $NH_2C(O)$-;

m is 0, 1 or 2 and

X is O or S.

3. The compound according claim 2 wherein:

R_1 and R_6 of the formula (Ia) or Formula (Ib) form:

a monocyclic 5 or 6 membered aromatic or nonaromatic heterocyclic ring optionally substituted by R_7;

a bicyclic ring having one 5, 6 or 7 membered aromatic or nonaromatic heterocyclic ring fused to a second 5-6 membered aromatic or nonaromatic heterocyclic or carbocyclic ring wherein each ring is optionally independently substituted by one or more R_7;

or a tricyclic ring having one 5, 6 or 7 membered aromatic or nonaromatic heterocyclic ring fused to a 5-6-membered aromatic or nonaromatic carbocyclic ring which in turn is fused to a 5, 6 or 7 membered aromatic or nonaromatic heterocyclic ring;

R_2 is hydrogen or methyl;

R_3 is a bond, hydrogen, C1-10 alkyl wherein one or more carbon atoms are optionally replaced by O, S or N, or R_3 is C2-5alkylene, C4-6 cycloalkyl, heterocyclylC1-5 alkyl wherein the heterocyclic moiety is selected from pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, 8-aza-bicyclo[3.2.1]octane, silinane, piperazinyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydrothiopyranyl and indolyl, or arylC1-2alkyl wherein R_3 is optionally substituted by one or more R_c;

R_c is C5-6 cycloalkyl, phenyl, naphthyl, indanyl, bicyclo[2.2.1]heptanyl, bicyclo[2.2.2]octanyl, bicyclo[4.1.0]heptanyl, bicyclo[3.1.0]hexanyl, bicyclo[1.1.1]pentanyl, spiroC8-10 cycloalkyl, cubanyl, 1,2,3,4-tetrahydronaphthyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, indolinyl, furanyl, tetrahydrofuranyl, pyranyl, tetrahydropyranyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, phenoxy, naphthyloxy, benzoyl,

phenoxycarbonyl, benzoyloxy, benzoylamino, phenylthio, aryloxycarbonylamino, arylcarbamoyloxy, arylsulfonylamino, arylaminosulfonyl, amino wherein the nitrogen atom may be independently mono or di-substituted by C1-5 alkyl or aryl, or R_c is halogen, hydroxy, oxo, carboxy, cyano, nitro, amidino or guanidino, R_c may be further optionally substituted by one or more R_d;

R_d is C1-3 alkyl, C3-6 cycloalkyl, phenyl, benzyl, C1-3 alkoxy, phenoxy, phenylC1-3alkoxy, benzoyl, halogen, hydroxy, oxo or cyano;

R_4 is hydrogen;

R_5 is hydrogen, C1-8 alkyl, C1-3 alkoxyC1-3 alkyl, C1-8 alkoxy, phenylC1-5 alkyl or naphthylC1-5 alkyl;

R_9 is hydrogen, C1-12 alkyl wherein one or more carbon atoms are optionally replaced by O, S or N, C3-7 cycloalkyl, heterocyclyl selected from pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl and indolinyl; heteroaryl selected from furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl, isoquinolinyl, quinazolinyl and quinoxalinyl, aryl or cyano, wherein R_9 is optionally substituted by one or more R_e;

R_e is selected from C1-5 alkyl, C3-7 cycloalkyl, aryl, aroyl, heterocyclyl selected from pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl and indolinyl; heteroaryl selected from furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl, isoquinolinyl, quinazolinyl and quinoxalinyl, halogen, hydroxy, oxo, carboxy, cyano, nitro, amidino and guanidino, R_e may be further optionally substituted by one or more R_f;

R_f is selected from C1-5 alkyl, C3-7 cycloalkyl, aryl optionally substituted by one or more groups selected from halogen, methyl or methoxy, heterocyclyl selected from pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl and indolinyl, heteroaryl selected from furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl, isoquinolinyl, quinazolinyl and quinoxalinyl, C1-5 alkoxy, aryloxy, aroyl, arylC1-5alkoxy, C1-5 alkoxycarbonyl, aryloxycarbonyl, C1-5 alkanoyloxy, aroyloxy, carbamoyl wherein the nitrogen atom may be independently mono or di-substituted by C1-5 alkyl, aryl, heterocyclyl selected from pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl and indolinyl or heteroaryl selected from furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl, isoquinolinyl, quinazolinyl and quinoxalinyl, C1-5 alkanoylamino, aroylamino, C1-5 alkylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, arylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, ureido wherein either nitrogen atom may be independently substituted by C1-5 alkyl, aryl, heterocyclyl selected from pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl and indolinyl, or heteroaryl selected from furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl, isoquinolinyl, quinazolinyl and quinoxalinyl, C1-5 alkoxycarbonylamino, aryloxycarbonylamino, C1-5 alkylcarbamoyloxy, arylcarbamoyloxy, C1-5 alkylsulfonylamino, arylsulfonylamino, C1-5 alkylaminosulfonyl, arylaminosulfonyl, amino wherein the nitrogen atom may be independently mono or di-substituted by C1-5 alkyl, aryl, heterocyclyl selected from pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl and indolinyl, or heteroaryl

selected from furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl, isoquinolinyl, quinazolinyl and quinoxalinyl, halogen, hydroxy, oxo, carboxy, cyano, nitro, amidino and guanidino;

or R_5 and R_9 together with the carbon they are attached form a 3 to 7-membered monocyclic carbocycle or a 7 to 14-membered bicyclic carbocycle optionally bridged, wherein either carbocycle is optionally benzofused and optionally substituted with one or more R_g;

R_g is selected from C1-5 alkyl, aryl, C1-5 alkoxycarbonyl, aryloxycarbonyl, arylC1-5alkoxycarbonyl, carbamoyl wherein the nitrogen atom may be optionally mono or di-substituted with a group selected from C1-5 alkyl, C3-7 cycloalkyl, aryl, arylC1-5alkyl, heterocyclyl selected from pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl and indolinyl, or heteroaryl selected from furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl, isoquinolinyl, quinazolinyl and quinoxalinyl, halogen, hydroxy, carboxy and cyano;

R_7 and R_8 are independently hydrogen, C1-4 alkyl, C5-6 cycloalkyl, C1-4 alkoxy, halogen, hydroxy, oxo, carboxy, nitrile, nitro or $NH_2C(O)$-;
and
X is O.

4. The compound according claim 3 wherein:

R_1 and R_6 of the formula (Ia) or formula (Ib) form:

a bicyclic ring having one 5 or 6 membered aromatic or nonaromatic heterocyclic ring fused to a second 5-6 membered heteroaryl, heterocycle or phenyl ring;

or a tricyclic ring having one 5, 6 or 7 membered aromatic or nonaromatic heterocyclic ring fused to a 5-6-membered aromatic or nonaromatic carbocyclic ring which in turn is fused to a 5, 6 or 7 membered aromatic or nonaromatic heterocyclic ring;
wherein each ring is optionally independently substituted by one or two R_7

R_2 is hydrogen;

R_3 is a bond, C1-10 alkyl wherein one or more carbon atoms are optionally replaced by O, S or N, or R_3 is C2-4alkylene, C5-6 cycloalkyl, heterocyclylC1-3 alkyl wherein the heterocyclic moiety is selected from pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, 8-aza-bicyclo[3.2.1]octane, silinane, piperazinyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydrothiopyranyl and indolyl, benzyl or naphthylmethyl wherein R_3 is optionally substituted by one or more R_c;

R_c is C5-6 cycloalkyl, phenyl, naphthyl, indanyl, bicyclo[2.2.1]heptanyl, bicyclo[2.2.2]octanyl, bicyclo[4.1.0]heptanyl, bicyclo[3.1.0]hexanyl, bicyclo[1.1.1]pentanyl, spiroC8-10 cycloalkyl, cubanyl, 1,2,3,4-tetrahydronaphthyl, furanyl, tetrahydropyranyl, thienyl, oxazolyl, thiazolyl, imidazolyl, pyrimidinyl, indolyl, benzofuranyl, benzothienyl, benzthiazolyl, phenoxy, naphthyloxy, benzoyl, phenoxycarbonyl, benzoyloxy, benzoylamino, phenylthio, phenoxycarbonylamino, arylcarbamoyloxy, phenylsulfonylamino, phenylaminosulfonyl, amino wherein the nitrogen atom may be independently mono or di-substituted by C1-3 alkyl or phenyl,
or R_c is halogen, hydroxy, oxo, carboxy or cyano, R_c may be further optionally substituted by one or more R_d;

R_d is methyl, cyclopropyl, cyclohexyl, phenyl, benzyl, methoxy, phenoxy, benzyloxy, benzoyl, fluoro, chloro, oxo or cyano;

R_5 is hydrogen, C1-5 alkyl, C1-3 alkoxyC1-3 alkyl, benzyl or phenethyl;

R_9 is hydrogen, C1-12 alkyl wherein one or more carbon atoms are optionally replaced by O, S or N, C3-7 cycloalkyl, heterocyclyl selected from pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl and indolinyl; heteroaryl selected from furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl, isoquinolinyl, quinazolinyl and quinoxalinyl, phenyl, naphthyl or cyano, wherein R_9 is optionally substituted by one or more R_e;.

R_e is selected from C1-5 alkyl, C3-7 cycloalkyl, phenyl, naphthyl, aroyl, heterocyclyl selected from pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl and indolinyl; heteroaryl selected from furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl, isoquinolinyl, quinazolinyl and quinoxalinyl, C1-5 alkoxy, aryloxy, aroyl, arylC1-5alkoxy, heteroarylC1-5alkoxy, C1-5 alkoxycarbonyl, aryloxycarbonyl, C1-5 alkanoyloxy, aroyloxy, carbamoyl wherein the nitrogen atom may be independently mono or di-substituted by C1-5 alkyl, aryl, heterocyclyl selected from piperidinyl, morpholinyl and piperazinyl or heteroaryl selected from furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl and isoquinolinyl, C1-5 alkanoylamino, aroylamino, C1-5 alkylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, arylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, arylC1-5 alkylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, ureido wherein either nitrogen atom may be independently substituted by C1-5 alkyl, aryl, heterocyclyl selected from piperidinyl, morpholinyl and piperazinyl or heteroaryl selected from furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, indolyl, benzofuranyl, benzothienyl,

benzimidazolyl, benzthiazolyl, quinolinyl and isoquinolinyl, halogen, hydroxy, oxo, nitro, carboxy and cyano, R_e may be further optionally substituted by one or more R_f;

R_f is selected from C1-5 alkyl, C3-7 cycloalkyl, phenyl optionally substituted by one or more groups selected from halogen, methyl or methoxy, naphthyl optionally substituted by one or more groups selected from halogen, methyl or methoxy, heterocyclyl selected from pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl and indolinyl; heteroaryl selected from furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl, isoquinolinyl, quinazolinyl and quinoxalinyl, C1-5 alkoxy, aryloxy, arylC1-5alkoxy, C1-5 alkoxycarbonyl, aryloxycarbonyl, C1-5 alkanoyloxy, aroyloxy, carbamoyl wherein the nitrogen atom may be independently mono or di-substituted by C1-5 alkyl, aryl, heterocyclyl selected from piperidinyl, morpholinyl and piperazinyl or heteroaryl selected from furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl and isoquinolinyl, C1-5 alkanoylamino, aroylamino, C1-5 alkylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, arylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, ureido wherein either nitrogen atom may be independently substituted by C1-5 alkyl, aryl, heterocyclyl selected from piperidinyl, morpholinyl and piperazinyl or heteroaryl selected from furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl and isoquinolinyl, C1-5 alkoxycarbonylamino, aryloxycarbonylamino, C1-5 alkylcarbamoyloxy, arylcarbamoyloxy, C1-5 alkylsulfonylamino, arylsulfonylamino, C1-5 alkylaminosulfonyl, arylaminosulfonyl, amino wherein the nitrogen atom may be

independently mono or di-substituted by C1-5 alkyl, aryl, heterocyclyl selected from pyrrolidinyl, piperidinyl, morpholinyl and piperazinyl or heteroaryl selected from furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl and isoquinolinyl, halogen, hydroxy, oxo, carboxy and cyano;

or R_5 and R_9 together with the carbon they are attached form a 3 to 7-membered monocyclic carbocycle or a 7 to 14-membered bicyclic carbocycle optionally bridged, wherein either carbocycle is optionally benzofused and optionally substituted with one or more R_g;

R_g is selected from C1-5 alkyl, phenyl, naphthyl, C1-5 alkoxycarbonyl, aryloxycarbonyl, arylC1-3alkoxycarbonyl, carbamoyl wherein the nitrogen atom may be optionally mono or di-substituted with a group selected from C1-5 alkyl, C3-6 cycloalkyl, phenyl, naphthyl, arylC1-3alkyl, heterocyclyl selected from pyrrolidinyl, piperidinyl, morpholinyl and piperazinyl or heteroaryl selected from furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl and isoquinolinyl, halogen, hydroxy, carboxy and cyano.

5. The compound according claim 4 wherein:

R_1 and R_6 of the formula (Ia) or Formula (Ib) form:
a bicyclic ring having one 5-6 membered aromatic or nonaromatic heterocyclic ring fused to a phenyl or 5-6 membered aromatic or nonaromatic heterocyclic ring;

a tricyclic ring having one 5-6 membered aromatic or nonaromatic heterocyclic ring fused to a 6-membered aromatic or nonaromatic carbocyclic ring which in turn is fused to a 5-6 membered aromatic or nonaromatic heterocyclic ring;

wherein each ring is optionally independently substituted by one or two R_7.

R_3 is a bond, C1-10 alkyl wherein one or more carbon atoms are optionally replaced by O, S or N, or R_3 is C2-4alkylene, C5-6 cycloalkyl, heterocyclylC1-2 alkyl wherein the heterocyclic moiety is selected from pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, 8-aza-bicyclo[3.2.1]octane, silinane, piperazinyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydrothiopyranyl and indolyl, benzyl or naphthylmethyl wherein R_3 is optionally substituted by one or more R_c;

R_c is C5-6 cycloalkyl, indanyl, bicyclo[2.2.1]heptanyl, bicyclo[2.2.2]octanyl, bicyclo[4.1.0]heptanyl, bicyclo[3.1.0]hexanyl, bicyclo[1.1.1]pentanyl, spiroC8-10 cycloalkyl, cubanyl, 1,2,3,4-tetrahydronaphthyl, thienyl, oxazolyl, thiazolyl, indolyl, benzofuranyl, benzothienyl, benzthiazolyl, phenoxy, benzoyl, phenoxycarbonyl, benzoyloxy, benzoylamino, phenylthio, phenoxycarbonylamino, phenylcarbamoyloxy, phenylsulfonylamino, phenylaminosulfonyl, amino wherein the nitrogen atom may be independently mono or di-substituted by methyl, ethyl or phenyl,
or R_c is fluoro, chloro or oxo, R_c may be further optionally substituted by one or more R_d;

R_d is methyl, cyclopropyl, phenyl, methoxy, fluoro, chloro or oxo;

R_9 is hydrogen, C1-12 alkyl wherein one or more carbon atoms are optionally replaced by O, S or N, C3-6 cycloalkyl, phenyl or cyano, wherein R_9 is optionally substituted by one or more R_e;

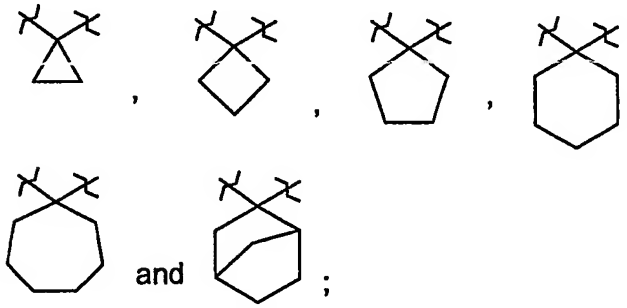
R_e is selected from C1-3 alkyl, C3-6 cycloalkyl, phenyl, naphthyl, aroyl, heterocyclyl selected from pyrrolidinyl, piperidinyl, morpholinyl, thio morpholinyl and piperazinyl; heteroaryl selected from furanyl, thienyl, pyrrolyl,

oxazolyl, thiazolyl, imidazolyl, pyridinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl and isoquinolinyl, C1-5 alkoxy, aryloxy, aroyl, arylC1-3alkoxy, heteroarylC1-3alkoxy, C1-5 alkoxycarbonyl, aryloxycarbonyl, C1-5 alkanoyloxy, aroyloxy, carbamoyl wherein the nitrogen atom may be independently mono or di-substituted by C1-5 alkyl, phenylor heteroaryl selected from furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl and indolyl, C1-5 alkanoylamino, aroylamino, C1-3 alkylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, arylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, arylC1-3alkylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, ureido wherein either nitrogen atom may be independently substituted by C1-5 alkyl or phenyl, C1-5 alkoxycarbonylamino, C1-5 alkylsulfonylamino, arylsulfonylamino, amino wherein the nitrogen atom may be independently mono or di-substituted by C1-5 alkyl, phenyl, naphthyl, heterocyclyl selected from piperidinyl, morpholinyl and piperazinyl or heteroaryl selected from furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, indolyl, halogen, hydroxy, oxo, nitro, carboxy and cyano, R_e may be further optionally substituted by one or more R_f;

R_f is selected from C1-3 alkyl, C5-6 cycloalkyl, phenyl optionally substituted by one or more groups selected from halogen or methyl, heterocyclyl selected from pyrrolidinyl, piperidinyl, morpholinyl and piperazinyl, heteroaryl selected from furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, pyrazinyl and indolyl, C1-5 alkoxy, aryloxy, arylC1-3alkoxy, C1-5 alkoxycarbonyl, aryloxycarbonyl, C1-5 alkanoyloxy, aroyloxy, carbamoyl wherein the nitrogen atom may be independently mono or di-substituted by C1-5 alkyl or aryl, C1-5 alkanoylamino, aroylamino, C1-5 alkylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, arylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, ureido wherein either nitrogen atom may be independently substituted by C1-5 alkyl or aryl, C1-5 alkoxycarbonylamino, aryloxycarbonylamino, C1-5 alkylcarbamoyloxy,

arylcarbamoyloxy, C1-5 alkylsulfonylamino, arylsulfonylamino, C1-5 alkylaminosulfonyl, arylaminosulfonyl, amino wherein the nitrogen atom may be independently mono or di-substituted by C1-5 alkyl or aryl, halogen, hydroxy, oxo, carboxy and cyano;

or R_5 and R_9 together with the carbon they are attached form a carbocyclic ring selected from :



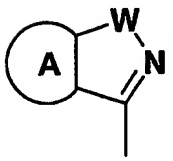
each carbocyclic ring being optionally benzofused and optionally substituted with one or more R_g;

R_g is selected from C1-5 alkyl, phenyl, C1-5 alkoxycarbonyl, aryloxycarbonyl, arylC1-3alkoxycarbonyl, carbamoyl wherein the nitrogen atom may be optionally mono or di-substituted with C1-5 alkyl, C3-6 cycloalkyl, phenyl, naphthyl or arylC1-3alkyl; halogen, hydroxy, carboxy and cyano.

6. The compound according claim 5 wherein::

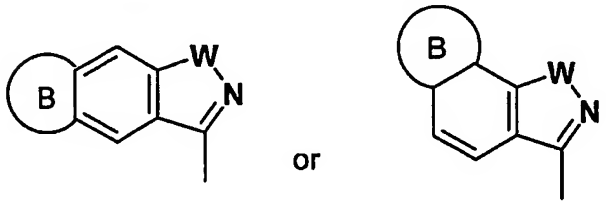
R_1 and R_6 of the formula (Ia) form:

the bicyclic ring:



; wherein W is $-S(O)_n-$, >C(O), -O-C(O)-, -S-C(O)- or -NH-C(O)-, n is 0, 1 or 2, fused ring A is selected from phenyl, morpholinyl, pyridinyl, pyrimidinyl, pyrazinyl, piperidinyl, pyrazolyl, pyrrolyl, pyrrolidinyl, imidazolyl, oxazolyl, thienyl, furanyl and thiazinyl and wherein each ring is optionally independently substituted by one or two R_7.

or the tricyclic ring:



wherein W is $-S(O)_n-$, >C(O), -O-C(O)-, -S-C(O)- or -NH-C(O)-, n is 0, 1 or 2, fused ring B is selected from phenyl, morpholinyl, pyridinyl, pyrimidinyl, pyrazinyl, piperidinyl, pyrazolyl, pyrrolyl, pyrrolidinyl, imidazolyl, oxazolyl, thienyl, furanyl and thiazinyl and wherein each ring is optionally independently substituted by one or two R_7.

R_3 is a bond, methyl, ethyl, n-propyl, propenyl, butenyl, i-butenyl, C1-5 alkoxyC1-5 alkyl, C1-5 alkoxycarbonylC1-5 alkyl, C1-5 alkylthioC1-5 alkyl, C1-5 alkylsulfinylC1-5 alkyl, C1-5 alkylsulfonylC1-5 alkyl, aminoC1-5 alkyl, mono or di-alkylaminoC1-5 alkyl, mono or di-alkylamidoC1-5 alkyl, cyclohexyl, heterocyclylC1-2 alkyl wherein the heterocyclic moiety is selected from pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, 8-aza-bicyclo[3.2.1]octane, silinane, piperazinyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydrothiopyranyl and indolyl, benzyl or naphthylmethyl wherein R_3 is optionally substituted by one or more R_c;

R_c is cyclohexyl, cyclopentyl, indanyl, bicyclo[2.2.1]heptanyl, bicyclo[2.2.2]octanyl, bicyclo[4.1.0]heptanyl, bicyclo[3.1.0]hexanyl, bicyclo[1.1.1]pentanyl, spiro[2.5] octanyl, spiro[3.5] nonyl, spiro[4.5] decanyl,

cubanyl, 1,2,3,4-tetrahydronaphthyl, phenoxy, benzoyl, phenoxycarbonyl, benzoyloxy, phenylthio, fluoro or chloro;

R_9 is hydrogen, C1-5 alkyl, C1-5 alkylene, C1-5 alkoxyC1-5 alkyl, C1-5 alkoxycarbonylC1-5 alkyl, C1-5 alkylthioC1-5 alkyl, C1-5 alkylsulfinylC1-5 alkyl, C1-5 alkylsulfonylC1-5 alkyl, aminoC1-5 alkyl, mono or di-C1-5alkylaminoC1-5 alkyl, mono or di-C1-5 alkylamidoC1-5 alkyl, phenyl, furanyl, thienyl, thiazolyl, imidazolyl, pyridinyl, indolyl or cyano wherein R_9 is optionally substituted by one to two groups of the formula R_e;

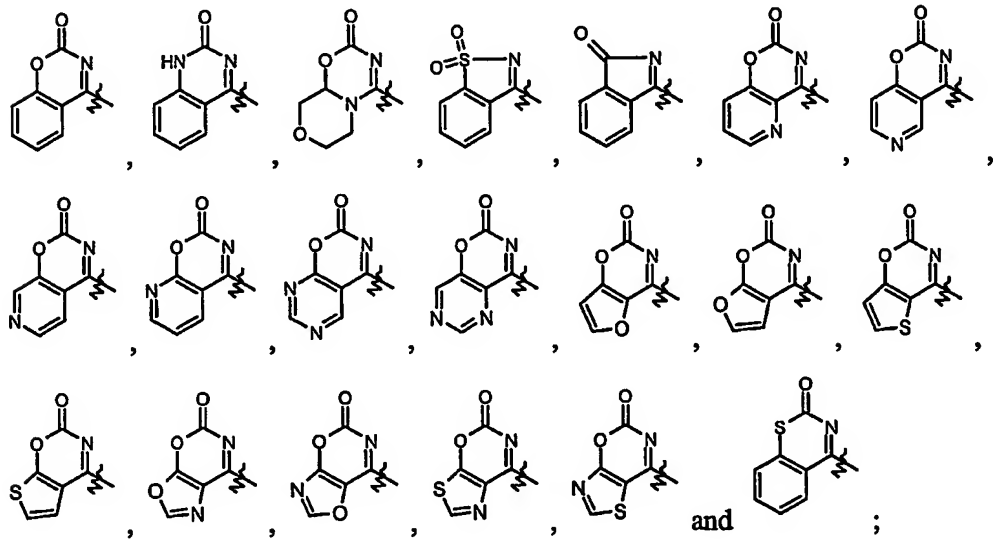
R_e is selected from C1-3 alkyl, C3-6 cycloalkyl, phenyl, naphthyl, benzoyl, furanyl, thienyl, thiazolyl, imidazolyl, pyridinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, indolyl, halogen, hydroxy, oxo, carboxy and cyano, R_e may be further optionally substituted by one or more R_f;

R_f is selected from C1-3 alkyl, phenyl optionally substituted by one or more groups selected from halogen and methyl, heterocyclyl selected from piperidinyl, morpholinyl and piperazinyl; heteroaryl selected from furanyl, thienyl, pyrrolyl and pyridinyl, C1-3 alkoxy, aryloxy, benzoyl, benzyloxy, C1-5 alkoxycarbonyl, C1-5 alkanoyloxy, aroyloxy, carbamoyl wherein the nitrogen atom may be independently mono or di-substituted by C1-5 alkyl or phenyl, C1-5 alkanoylamino, aroylamino, C1-5 alkylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, ureido wherein either nitrogen atom may be independently substituted by C1-5 alkyl or phenyl, C1-5 alkoxycarbonylamino, C1-5 alkylcarbamoyloxy, arylcarbamoyloxy, C1-3 alkylsulfonylamino, arylsulfonylamino, C1-3 alkylaminosulfonyl, arylaminosulfonyl, amino wherein the nitrogen atom may be independently mono or di-substituted by C1-3 alkyl or phenyl, halogen, hydroxy, oxo, nitro, carboxy and cyano;

R_g is selected from C1-3 alkyl, phenyl, C1-3 alkoxycarbonyl, phenoxyoxycarbonyl, benzyloxy, carbamoyl wherein the nitrogen atom may be optionally mono or di-substituted with a group selected from C1-5 alkyl, phenyl and benzyl, halogen, hydroxy, carboxy and cyano.

7. The compound according claim 6 wherein:

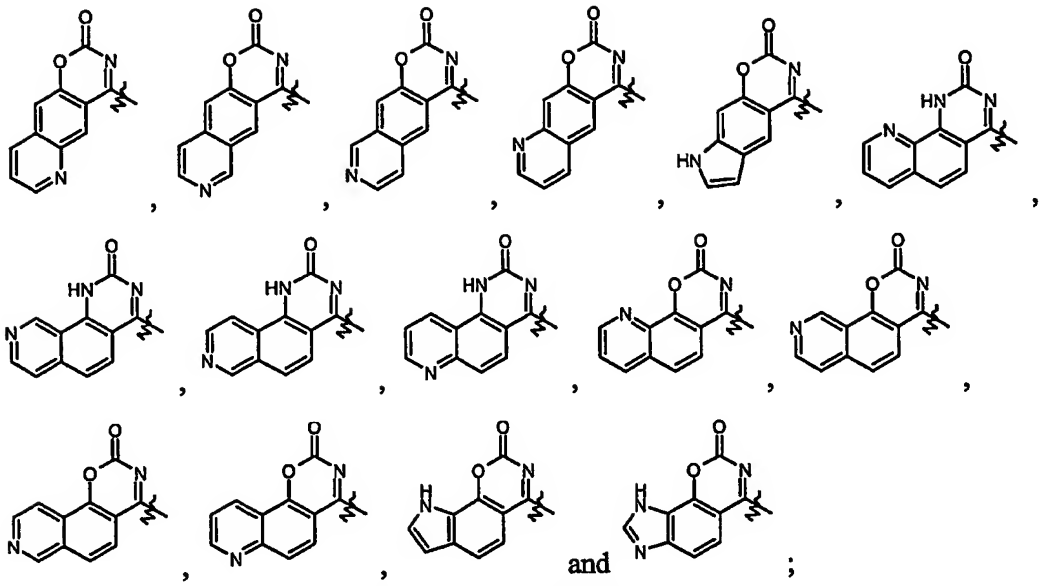
R_1 and R_6 of the formula (Ia) form the bicyclic ring selected from:



and

;

or R_1 and R_6 of the formula (Ia) form the tricyclic ring selected from:



wherein each ring is optionally independently substituted by one or two R_7;

R_3 is methyl, ethyl, n-propyl, propenyl, butenyl, i-butenyl, C1-3 alkoxyC1-3 alkyl, C1-3 alkoxycarbonylC1-3 alkyl, C1-3 alkylthioC1-3 alkyl, C1-3 alkylsulfinylC1-3 alkyl, C1-3 alkylsulfonylC1-3 alkyl, aminoC1-3 alkyl, mono or di-C1-3 alkylaminoC1-3 alkyl, mono or di-C1-3 alkylamidoC1-3 alkyl, heterocyclylC1-2 alkyl wherein the heterocyclic moiety is selected from pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, 8-aza-bicyclo[3.2.1]octane, silinane, piperazinyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydrothiopyranyl and indolyl, benzyl or naphthylmethyl wherein R_3 is optionally substituted by one to two R_c;

R_c is methyl, cyclohexyl, cyclopentyl, indanyl, 1,2,3,4-tetrahydronaphthyl, spiro[2.5] octanyl, spiro[3.5] nonyl, spiro[4.5] decanyl, fluoro or chloro;

R_9 is hydrogen, C1-4 alkyl, C1-5 alkylene, C1-3 alkoxyC1-3 alkyl, C1-3 alkoxycarbonylC1-3 alkyl, C1-3 alkylthioC1-3 alkyl, C1-3 alkylsulfinylC1-3 alkyl, C1-3 alkylsulfonylC1-3 alkyl, aminoC1-3 alkyl, mono or di-C1-3 alkylaminoC1-3 alkyl, mono or di-C1-3 alkylamidoC1-3 alkyl, phenyl, furanyl, thienyl, thiazolyl, imidazolyl,

pyridinyl, indolyl or cyano wherein R_9 is optionally substituted by one to two groups of the formula R_e;

R_e is selected from methyl, C3-6 cycloalkyl, phenyl, benzoyl, naphthyl, furanyl, thienyl, thiazolyl, imidazolyl, pyridinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, indolyl, halogen, hydroxy, carboxy and cyano, R_e may be further optionally substituted by one or more R_f;

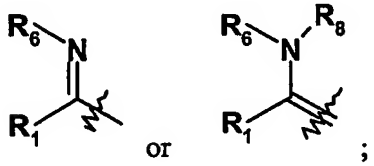
R_f is selected from C1-3 alkyl, phenyl or phenylsulfonyl each optionally substituted by one or more groups selected from halogen or methyl, C1-3 alkoxy, aryloxy, benzoyl, benzyloxy, C1-3 alkoxycarbonyl, carbamoyl wherein the nitrogen atom may be independently mono or di-substituted by C1-3 alkyl or phenyl, C1-5 alkanoylamino, aroylamino, amino wherein the nitrogen atom may be independently mono or di-substituted by C1-3 alkyl or phenyl, halogen, hydroxy, oxo, nitro, carboxy and cyano;

and

R_g is selected from C1-3 alkyl, phenyl, C1-3 alkoxycarbonyl, benzyloxy and carboxy.

8. The compound according claim 1 wherein:

R_1 and R_6 remain acyclic:



;

R_1 is a bond, C1-5 alkyl, C1-5 alkoxy, C3-6 cycloalkyl, aryloxy, phenyl, benzyl, naphthyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, furanyl, thienyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, indolyl, quinolinyl, benzofuranyl, benzthienyl, benzimidazolyl, benzthiazolyl, benzoxazolyl or amino; wherein R_1 is optionally substituted by one or more R_a;

R_a is a bond, C1-3 alkyl, cyclopropyl, cyclohexyl, phenyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, thienyl, imidazolyl, C1-3 alkoxy, C1-3alkanoyl, C1-3alkanoyloxy, aryloxy, benzyloxy, C1-3 alkoxycarbonyl, aryloxycarbonyl, aroyloxy, carbamoyl wherein the nitrogen atom may be independently mono or di-substituted by C1-3 alkyl, aryl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl or piperazinyl,
or R_a is C1-3 alkanoylamino, aroylamino, C1-3 alkylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, arylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, ureido wherein either nitrogen atom may be independently substituted by C1-3 alkyl, aryl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl or piperazinyl,
or R_a is C1-3 alkoxycarbonylamino, aryloxycarbonylamino, C1-3 alkylcarbamoyloxy, arylcarbamoyloxy, C1-3 alkylsulfonylamino, arylsulfonylamino, C1-3 alkylaminosulfonyl, arylaminosulfonyl, amino wherein the nitrogen atom may be independently mono or di-substituted by C1-3 alkyl, aryl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl or piperazinyl,
or R_a is halogen, hydroxy, oxo, carboxy, cyano, nitro, carboxamide, amidino or guanidino, R_a may be further optionally substituted by one or more R_b;

R_b is methyl, ethyl, n-propyl, i-propyl, cyclopropyl, cyclopentyl, cyclohexyl, phenyl, methoxy, ethoxy, n-propoxy, i-propoxy, phenoxy, benzyloxy, fluoro, chloro, bromo, iodo, hydroxy, oxo, carboxy, cyano, nitro or carboxamide;

R_2 is hydrogen or methyl or ethyl;

R_3 is a bond, hydrogen, C1-10 alkyl wherein one or more carbon atoms are optionally replaced by O, S or N, or R_3 is C2-5alkylene, C3-7 cycloalkyl, heterocyclylC1-5 alkyl wherein the heterocyclic moiety is selected from pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, 8-aza-bicyclo[3.2.1]octane, silinane, piperazinyl, indolinyl, furanyl,

tetrahydrofuranyl, pyranyl, tetrahydropyranyl, tetrahydrothiopyranyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, pyridinyl, pyrimidinyl, pyrazinyl and indolyl, arylC1-3alkyl or aryl wherein R_3 is optionally substituted by one or more R_c;

R_c is C3-7 cycloalkyl, aryl, indanyl, indenyl, bicyclo[2.2.1]heptanyl, bicyclo[2.2.2]octanyl, bicyclo[4.1.0]heptanyl, bicyclo[3.1.0]hexanyl, bicyclo[1.1.1]pentanyl, spiroC8-10 cycloalkyl, cubanyl, 1,2,3,4-tetrahydronaphthyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, indolinyl, furanyl, tetrahydrofuranyl, pyranyl, tetrahydropyranyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, aryloxy, aroyl, aryloxycarbonyl, aroyloxy,
or R_c is aroylamino, arylthio, aryloxycarbonylamino, arylcarbamoyloxy, arylsulfonylamino, arylaminosulfonyl, amino wherein the nitrogen atom may be independently mono or di-substituted by C1-5 alkyl, aryl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, indolinyl, furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl, isoquinolinyl, quinazolinyl or quinoxalinyl,
or R_c is halogen, hydroxy, oxo, carboxy, cyano, nitro, amidino or guanidino, R_c may be further optionally substituted by one or more R_d;
R_d is C1-5 alkyl, C3-6 cycloalkyl, aryl, arylC1-4 alkyl, C1-5 alkoxy, aryloxy, arylC1-5alkoxy, aroyl, halogen, hydroxy, oxo or cyano;

R_4 is hydrogen or methyl;

R_9 is hydrogen, C1-12 alkyl wherein one or more carbon atoms are optionally replaced by O, S or N, C3-7 cycloalkyl, heterocyclyl selected from pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl and indolinyl, heteroaryl selected from furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl,

isothiazolyl, oxadiazolyl, triazolyl, tetrazolyl, thiadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, indolyl, isoindolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, purinyl, quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, carbazolyl, phenothiazinyl and phenoxazinyl, aryl or cyano, wherein R_9 is optionally substituted by one or more R_e;

R_e is selected from C1-8 alkyl, C3-7 cycloalkyl, aryl, aroyl, heterocyclyl selected from pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl and indolinyl; heteroaryl selected from furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, tetrazolyl, thiadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, indolyl, isoindolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, purinyl, quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, carbazolyl, phenothiazinyl and phenoxazinyl, halogen, hydroxy, oxo, carboxy, cyano, nitro, amidino and guanidino, R_e may be further optionally substituted by one or more R_f;

R_f is selected from C1-8 alkyl, C3-7 cycloalkyl, aryl optionally substituted by one or more groups selected from halogen, methyl or methoxy, heterocyclyl selected from pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl and indolinyl; heteroaryl selected from furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, tetrazolyl, thiadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, indolyl, isoindolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, purinyl, quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, carbazolyl, phenothiazinyl and phenoxazinyl, C1-8 alkoxy, aryloxy, aroyl, arylC1-8alkoxy, C1-8 alkoxycarbonyl, aryloxycarbonyl, C1-8 alkanoyloxy, aroyloxy, carbamoyl wherein the nitrogen atom may be independently mono or di-substituted by C1-8 alkyl, aryl, heterocyclyl selected from pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl and indolinyl, or heteroaryl selected from furanyl, thienyl, pyrrolyl, oxazolyl,

thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, tetrazolyl, thiadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, indolyl, isoindolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, purinyl, quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, carbazolyl, phenothiazinyl and phenoxazinyl, C1-8 alkanoylamino, aroylamino, C1-8 alkylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, arylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, ureido wherein either nitrogen atom may be independently substituted by alkyl, aryl, heterocyclyl selected from pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl and indolinyl, or heteroaryl selected from furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, tetrazolyl, thiadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, indolyl, isoindolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, purinyl, quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, carbazolyl, phenothiazinyl and phenoxazinyl, alkoxycarbonylamino, aryloxycarbonylamino, alkylcarbamoyloxy, arylcarbamoyloxy, alkylsulfonylamino, arylsulfonylamino, alkylaminosulfonyl, arylaminosulfonyl, amino wherein the nitrogen atom may be independently mono or di-substituted by alkyl, aryl, heterocyclyl selected from pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl and indolinyl, or heteroaryl selected from furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, tetrazolyl, thiadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, indolyl, isoindolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, purinyl, quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, carbazolyl, phenothiazinyl and phenoxazinyl, halogen, hydroxy, oxo, carboxy, cyano, nitro, amidino and guanidino;

or R_5 and R_9 together with the carbon they are attached form a 3 to 7-membered monocyclic carbocycle or a 7 to 14-membered bicyclic carbocycle optionally bridged, wherein either carbocycle is optionally benzofused and optionally substituted with one or more R_g;

R_g is selected from C1-8 alkyl, aryl, C1-8 alkoxycarbonyl, aryloxycarbonyl, arylC1-8alkoxycarbonyl, carbamoyl wherein the nitrogen atom may be optionally mono or di-substituted with a group selected from C1-8 alkyl, C3-7 cycloalkyl, aryl, arylC1-8alkyl, heterocyclyl selected from pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl and indolinyl, or heteroaryl selected from furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, tetrazolyl, thiadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, indolyl, isoindolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, purinyl, quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, carbazolyl, phenothiazinyl and phenoxazinyl, halogen, hydroxy, carboxy and cyano;

R_6 is

hydroxy, nitrile or

a C1-5 saturated or unsaturated branched or unbranched alkyl optionally partially or fully halogenated wherein one or more C atoms are optionally replaced by O, NH, or $S(O)_2$ and wherein said chain is optionally independently substituted with 1-2 oxo groups, -NH_2, one or more C1-4 alkyl, C3-6 cycloalkyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, indolinyl, pyranyl, thiopyranyl, furanyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl, isoquinolinyl, quinazolinyl, benzoxazolyl or quinoxalinyl;

R_8 is hydrogen, C1-5 alkyl, C3-6 cycloalkyl, aryl, C1-5 alkoxy, aryloxy, benzyloxy each of the aforementioned are optionally halogenated or hydroxy;

and

X is O.

9. The compound according claim 8 wherein:

R_1 is a bond, methyl, ethyl, i-propyl, methoxy, ethoxy, cyclopropyl, cyclopentyl, cyclohexyl, phenoxy, phenyl, benzyl, naphthyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, furanyl, thienyl, thiazolyl, imidazolyl, pyridinyl, pyrazinyl or amino; wherein R_1 is optionally substituted by one or more R_a;

R_a is a bond, methyl, ethyl, cyclopropyl, phenyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, thienyl, imidazolyl, methoxy, acetyl, acetoxy, phenoxy, benzyloxy, methoxycarbonyl, phenoxycarbonyl, benzoyloxy, carbamoyl wherein the nitrogen atom may be independently mono or di-substituted by methyl, ethyl or phenyl,
or R_a is acetylamino, benzoylamino, methylthio, phenylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, ureido wherein either nitrogen atom may be independently substituted by methyl, ethyl or phenyl,
or R_a is methoxycarbonylamino, phenoxycarbonylamino, methylcarbamoyloxy, phenylcarbamoyloxy, methylsulfonylamino, phenylsulfonylamino, methylaminosulfonyl, phenylaminosulfonyl, amino wherein the nitrogen atom may be independently mono or di-substituted by methyl or phenyl,
or R_a is fluoro, chloro, bromo, iodo, hydroxy, oxo, carboxy, cyano, nitro or carboxamide, R_a may be further optionally substituted by one or more R_b;

R_b is methyl, cyclopropyl, phenyl, methoxy, phenoxy, benzyloxy, fluoro, chloro, hydroxy, oxo, carboxy or carboxamide;

R_3 is a bond, hydrogen, C1-10 alkyl wherein one or more carbon atoms are optionally replaced by O, S or N, or R_3 is C2-5alkylene, C4-6 cycloalkyl, heterocyclylC1-5 alkyl wherein the heterocyclic moiety is selected from pyrrolidinyl, piperidinyl, morpholinyl,

thiomorpholinyl, 8-aza-bicyclo[3.2.1]octane, silinane, piperazinyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydrothiopyranyl and indolyl, or arylC1-2alkyl wherein R_3 is optionally substituted by one or more R_c;

R_c is C5-6 cycloalkyl, phenyl, naphthyl, indanyl, bicyclo[2.2.1]heptanyl, bicyclo[2.2.2]octanyl, bicyclo[4.1.0]heptanyl, bicyclo[3.1.0]hexanyl, bicyclo[1.1.1]pentanyl, spiroC8-10 cycloalkyl, cubanyl, 1,2,3,4-tetrahydronaphthyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, indolinyl, furanyl, tetrahydrofuranyl, pyranyl, tetrahydropyranyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, phenoxy, naphthyloxy, benzoyl, phenoxycarbonyl, benzoyloxy, benzoylamino, phenylthio, aryloxycarbonylamino, arylcarbamoyloxy, arylsulfonylamino, arylaminosulfonyl, amino wherein the nitrogen atom may be independently mono or di-substituted by C1-5 alkyl or aryl, or R_c is halogen, hydroxy, oxo, carboxy, cyano, nitro, amidino or guanidino, R_c may be further optionally substituted by one or more R_d;

R_d is C1-3 alkyl, C3-6 cycloalkyl, phenyl, benzyl, C1-3 alkoxy, phenoxy, phenylC1-3alkoxy, benzoyl, halogen, hydroxy, oxo or cyano;

R_5 is hydrogen, C1-8 alkyl, C1-3 alkoxyC1-3 alkyl, C1-8 alkoxy, C1-5phenyl or C1-5naphthyl;

R_9 is hydrogen, C1-12 alkyl wherein one or more carbon atoms are optionally replaced by O, S or N, C3-7 cycloalkyl, heterocyclyl selected from pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl and indolinyl; heteroaryl selected from furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl,

benzthiazolyl, quinolinyl, isoquinolinyl, quinazolinyl and quinoxalinyl, aryl or cyano, wherein R_9 is optionally substituted by one or more R_e;

R_e is selected from C1-5 alkyl, C3-7 cycloalkyl, aryl, aroyl, heterocyclyl selected from pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl and indolinyl; heteroaryl selected from furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl, isoquinolinyl, quinazolinyl and quinoxalinyl, halogen, hydroxy, oxo, carboxy, cyano, nitro, amidino and guanidino, R_e may be further optionally substituted by one or more R_f;

R_f is selected from C1-5 alkyl, C3-7 cycloalkyl, aryl optionally substituted by one or more groups selected from halogen, methyl or methoxy, heterocyclyl selected from pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl and indolinyl, heteroaryl selected from furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl, isoquinolinyl, quinazolinyl and quinoxalinyl, C1-5 alkoxy, aryloxy, aroyl, arylC1-5alkoxy, C1-5 alkoxycarbonyl, aryloxycarbonyl, C1-5 alkanoyloxy, aroyloxy, carbamoyl wherein the nitrogen atom may be independently mono or di-substituted by C1-5 alkyl, aryl, heterocyclyl selected from pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl and indolinyl or heteroaryl selected from furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl, isoquinolinyl, quinazolinyl and quinoxalinyl, C1-5 alkanoylamino, aroylamino, C1-5 alkylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, arylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, ureido wherein either nitrogen

atom may be independently substituted by C1-5 alkyl, aryl, heterocyclyl selected from pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl and indolinyl, or heteroaryl selected from furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl, isoquinolinyl, quinazolinyl and quinoxalinyl, C1-5 alkoxycarbonylamino, aryloxycarbonylamino, C1-5 alkylcarbamoyloxy, arylcarbamoyloxy, C1-5 alkylsulfonylamino, arylsulfonylamino, C1-5 alkylaminosulfonyl, arylaminosulfonyl, amino wherein the nitrogen atom may be independently mono or di-substituted by C1-5 alkyl, aryl, heterocyclyl selected from pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl and indolinyl, or heteroaryl selected from furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl, isoquinolinyl, quinazolinyl and quinoxalinyl, halogen, hydroxy, oxo, carboxy, cyano, nitro, amidino and guanidino;

or R_5 and R_9 together with the carbon they are attached form a 3 to 7-membered monocyclic carbocycle or a 7 to 14-membered bicyclic carbocycle optionally bridged, wherein either carbocycle is optionally benzofused and optionally substituted with one or more R_g;

R_g is selected from C1-5 alkyl, aryl, C1-5 alkoxycarbonyl, aryloxycarbonyl, arylC1-5alkoxycarbonyl, carbamoyl wherein the nitrogen atom may be optionally mono or di-substituted with a group selected from C1-5 alkyl, C3-7 cycloalkyl, aryl, arylC1-5alkyl, heterocyclyl selected from pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl and indolinyl, or heteroaryl selected from furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl, isoquinolinyl, quinazolinyl and quinoxalinyl, halogen, hydroxy, carboxy and cyano;

R_6 is
nitrile or
a C1-5 saturated or unsaturated branched or unbranched alkyl optionally partially or fully halogenated wherein one or more C atoms are optionally replaced by O, NH, or $S(O)_2$ and wherein said chain is optionally independently substituted with oxo, $-NH_2$, C3-6 cycloalkyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, pyridinyl, pyrimidinyl or pyrazinyl; and

R_8 is hydrogen, C1-3 alkyl, C3-6 cycloalkyl, phenyl, C1-3 alkoxy, benzyloxy each of the aforementioned are optionally halogenated or hydroxy.

10. The compound according claim 9 wherein:

R_1 is a bond, methyl, ethyl, i-propyl, methoxy, cyclopropyl, cyclohexyl, phenoxy, phenyl, benzyl, naphthyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, furanyl, thienyl, thiazolyl, imidazolyl, pyridinyl, pyrazinyl or amino; wherein R_1 is optionally substituted by one or more R_a;

R_a is methyl, phenyl, thienyl, methoxy, acetyl, acetoxy, phenoxy, benzyloxy, methoxycarbonyl, benzoyloxy, carbamoyl wherein the nitrogen atom may be independently mono or di-substituted by methyl or phenyl,
or R_a is acetylamino, methylthio, phenylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, ureido wherein either nitrogen atom may be independently substituted by methyl or phenyl,
or R_a is methoxycarbonylamino, methylcarbamoyloxy, phenylcarbamoyloxy, methylsulfonylamino, phenylsulfonylamino, amino wherein the nitrogen atom may be independently mono or di-substituted by methyl or phenyl,
or R_a is fluoro, chloro, hydroxy, oxo, carboxy, cyano or carboxamide;

R_3 is a bond, C1-10 alkyl wherein one or more carbon atoms are optionally replaced by O, S or N, or R_3 is C2-4alkylene, C5-6 cycloalkyl, heterocyclylC1-3 alkyl wherein the heterocyclic moiety is selected from pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, 8-aza-bicyclo[3.2.1]octane, silinane, piperazinyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydrothiopyranyl and indolyl, benzyl or naphthylmethyl wherein R_3 is optionally substituted by one or more R_c;

R_c is C5-6 cycloalkyl, phenyl, naphthyl, indanyl, bicyclo[2.2.1]heptanyl, bicyclo[2.2.2]octanyl, bicyclo[4.1.0]heptanyl, bicyclo[3.1.0]hexanyl, bicyclo[1.1.1]pentanyl, spiroC8-10 cycloalkyl, cubanyl, 1,2,3,4-tetrahydronaphthyl, furanyl, tetrahydropyranyl, thienyl, oxazolyl, thiazolyl, imidazolyl, pyrimidinyl, indolyl, benzofuranyl, benzothienyl, benzthiazolyl, phenoxy, naphthyloxy, benzoyl, phenoxycarbonyl, benzoyloxy, benzoylamino, phenylthio, phenoxycarbonylamino, arylcarbamoyloxy, phenylsulfonylamino, phenylaminosulfonyl, amino wherein the nitrogen atom may be independently mono or di-substituted by C1-3 alkyl or phenyl,
or R_c is halogen, hydroxy, oxo, carboxy or cyano, R_c may be further optionally substituted by one or more R_d;

R_d is methyl, cyclopropyl, cyclohexyl, phenyl, benzyl, methoxy, phenoxy, benzyloxy, benzoyl, fluoro, chloro, oxo or cyano;

R_5 is hydrogen, C1-5 alkyl, C1-3 alkoxyC1-3 alkyl, benzyl or phenethyl;

R_9 is hydrogen, C1-12 alkyl wherein one or more carbon atoms are optionally replaced by O, S or N, C3-7 cycloalkyl, heterocyclyl selected from pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl and indolinyl; heteroaryl selected from furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl, isoquinolinyl, quinazolinyl and quinoxalinyl, phenyl, naphthyl or cyano, wherein R_9 is optionally substituted by one or more R_e;.

R_e is selected from C1-5 alkyl, C3-7 cycloalkyl, phenyl, naphthyl, aroyl, heterocyclyl selected from pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl and indolinyl; heteroaryl selected from furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl, isoquinolinyl, quinazolinyl and quinoxalinyl, C1-5 alkoxy, aryloxy, aroyl, arylC1-5alkoxy, heteroarylC1-5alkoxy, C1-5 alkoxycarbonyl, aryloxycarbonyl, C1-5 alkanoyloxy, aroyloxy, carbamoyl wherein the nitrogen atom may be independently mono or di-substituted by C1-5 alkyl, aryl, heterocyclyl selected from piperidinyl, morpholinyl and piperazinyl or heteroaryl selected from furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl and isoquinolinyl, C1-5 alkanoylamino, aroylamino, C1-5 alkylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, arylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, arylC1-5 alkylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, ureido wherein either nitrogen atom may be independently substituted by C1-5 alkyl, aryl, heterocyclyl selected from piperidinyl, morpholinyl and piperazinyl or heteroaryl selected from furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl and isoquinolinyl, halogen, hydroxy, oxo, nitro, carboxy and cyano, R_e may be further optionally substituted by one or more R_f;

R_f is selected from C1-5 alkyl, C3-7 cycloalkyl, phenyl optionally substituted by one or more groups selected from halogen, methyl or methoxy, naphthyl optionally substituted by one or more groups selected from halogen, methyl or methoxy, heterocyclyl selected from pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl and indolinyl; heteroaryl selected from furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl,

imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl, isoquinolinyl, quinazolinyl and quinoxalinyl, C1-5 alkoxy, aryloxy, arylC1-5alkoxy, C1-5 alkoxycarbonyl, aryloxycarbonyl, C1-5 alkanoyloxy, aroyloxy, carbamoyl wherein the nitrogen atom may be independently mono or di-substituted by C1-5 alkyl, aryl, heterocyclyl selected from piperidinyl, morpholinyl and piperazinyl or heteroaryl selected from furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl and isoquinolinyl, C1-5 alkanoylamino, aroylamino, C1-5 alkylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, arylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, ureido wherein either nitrogen atom may be independently substituted by C1-5 alkyl, aryl, heterocyclyl selected from piperidinyl, morpholinyl and piperazinyl or heteroaryl selected from furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl and isoquinolinyl, C1-5 alkoxycarbonylamino, aryloxycarbonylamino, C1-5 alkylcarbamoyloxy, arylcarbamoyloxy, C1-5 alkylsulfonylamino, arylsulfonylamino, C1-5 alkylaminosulfonyl, arylaminosulfonyl, amino wherein the nitrogen atom may be independently mono or di-substituted by C1-5 alkyl, aryl, heterocyclyl selected from pyrrolidinyl, piperidinyl, morpholinyl and piperazinyl or heteroaryl selected from furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl and isoquinolinyl, halogen, hydroxy, oxo, carboxy and cyano;

or R_5 and R_9 together with the carbon they are attached form a 3 to 7-membered monocyclic carbocycle or a 7 to 14-membered bicyclic carbocycle optionally bridged,

wherein either carbocycle is optionally benzofused and optionally substituted with one or more R_g;

R_g is selected from C1-5 alkyl, phenyl, naphthyl, C1-5 alkoxycarbonyl, aryloxycarbonyl, arylC1-3alkoxycarbonyl, carbamoyl wherein the nitrogen atom may be optionally mono or di-substituted with a group selected from C1-5 alkyl, C3-6 cycloalkyl, phenyl, naphthyl, arylC1-3alkyl, heterocyclyl selected from pyrrolidinyl, piperidinyl, morpholinyl and piperazinyl or heteroaryl selected from furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyi, pyridinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl and isoquinolinyl, halogen, hydroxy, carboxy and cyano;

R_6 is
nitrile or
a C1-5 saturated or unsaturated branched or unbranched alkyl optionally partially or fully halogenated wherein one or more C atoms are optionally replaced by O, NH, or $S(O)_2$ and wherein said chain is optionally independently substituted with oxo, $-NH_2$, C3-6 cycloalkyl, morpholinyl or piperazinyl; and

R_8 is hydrogen, C1-3 alkyl, C1-3 alkoxy or hydroxy.

11. The compound according claim 10 wherein:

R_1 is i-propyl, benzyloxy, cyclohexyl, phenyl, 4-(acetylamino)-phenyl, 4-(methanesulfonylamino)-phenyl, 4-methoxyphenyl, 3-phenoxyphenyl, 4-chlorophenyl, 4-fluorophenyl, 2-fluorophenyl, 2-fluoro-4-chlorophenyl, naphthyl, thienylmethyl, piperidinyl, morpholinyl, pyrrolidinyl, piperazinyl, furanyl, thienyl, 5-chlorothienyl, pyridin-4-yl, pyrazinyl, methylamino, ethylamino, dimethylamino or diethylamino;

R_3 is a bond, C1-10 alkyl wherein one or more carbon atoms are optionally replaced by O, S or N, or R_3 is C2-4alkylene, C5-6 cycloalkyl, heterocyclylC1-2 alkyl wherein the heterocyclic moiety is selected from pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, 8-aza-bicyclo[3.2.1]octane, silinane, piperazinyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydrothiopyranyl and indolyl, benzyl or naphthylmethyl wherein R_3 is optionally substituted by one or more R_c;

R_c is C5-6 cycloalkyl, indanyl, bicyclo[2.2.1]heptanyl, bicyclo[2.2.2]octanyl, bicyclo[4.1.0]heptanyl, bicyclo[3.1.0]hexanyl, bicyclo[1.1.1]pentanyl, spiroC8-10 cycloalkyl, cubanyl, 1,2,3,4-tetrahydronaphthyl, thienyl, oxazolyl, thiazolyl, indolyl, benzofuranyl, benzothienyl, benzthiazolyl, phenoxy, benzoyl, phenoxycarbonyl, benzoyloxy, benzoylamino, phenylthio, phenoxycarbonylamino, phenylcarbamoyloxy, phenylsulfonylamino, phenylaminosulfonyl, amino wherein the nitrogen atom may be independently mono or di-substituted by methyl, ethyl or phenyl,
or R_c is fluoro, chloro or oxo, R_c may be further optionally substituted by one or more R_d;

R_d is methyl, cyclopropyl, phenyl, methoxy, fluoro, chloro or oxo;

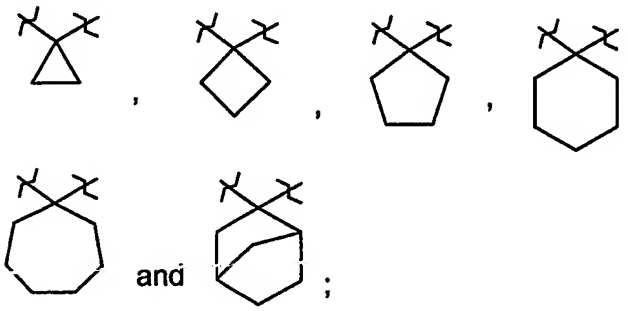
R_9 is hydrogen, C1-12 alkyl wherein one or more carbon atoms are optionally replaced by O, S or N, C3-6 cycloalkyl, phenyl or cyano, wherein R_9 is optionally substituted by one or more R_e;

R_e is selected from C1-3 alkyl, C3-6 cycloalkyl, phenyl, naphthyl, aroyl, heterocyclyl selected from pyrrolidinyl, piperidinyl, morpholinyl, thio morpholinyl and piperazinyl; heteroaryl selected from furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl and isoquinolinyl, C1-5 alkoxy, aryloxy, aroyl, arylC1-3alkoxy, heteroarylC1-3alkoxy, C1-5 alkoxycarbonyl, aryloxycarbonyl, C1-5 alkanoyloxy, aroyloxy, carbamoyl wherein the nitrogen

atom may be independently mono or di-substituted by C1-5 alkyl, phenylor heteroaryl selected from furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl and indolyl, C1-5 alkanoylamino, aroylamino, C1-3 alkylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, arylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, arylC1-3alkylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, ureido wherein either nitrogen atom may be independently substituted by C1-5 alkyl or phenyl, C1-5 alkoxycarbonylamino, C1-5 alkylsulfonylamino, arylsulfonylamino, amino wherein the nitrogen atom may be independently mono or di-substituted by C1-5 alkyl, phenyl, naphthyl, heterocyclyl selected from piperidinyl, morpholinyl and piperazinyl or heteroaryl selected from furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, indolyl, halogen, hydroxy, oxo, nitro, carboxy and cyano, R_e may be further optionally substituted by one or more R_f;

R_f is selected from C1-3 alkyl, C5-6 cycloalkyl, phenyl optionally substituted by one or more groups selected from halogen or methyl, heterocyclyl selected from pyrrolidinyl, piperidinyl, morpholinyl and piperazinyl, heteroaryl selected from furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, pyrazinyl and indolyl, C1-5 alkoxy, aryloxy, arylC1-3alkoxy, C1-5 alkoxycarbonyl, aryloxycarbonyl, C1-5 alkanoyloxy, aroyloxy, carbamoyl wherein the nitrogen atom may be independently mono or di-substituted by C1-5 alkyl or aryl, C1-5 alkanoylamino, aroylamino, C1-5 alkylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, arylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, ureido wherein either nitrogen atom may be independently substituted by C1-5 alkyl or aryl, C1-5 alkoxycarbonylamino, aryloxycarbonylamino, C1-5 alkylcarbamoyloxy, arylcarbamoyloxy, C1-5 alkylsulfonylamino, arylsulfonylamino, C1-5 alkylaminosulfonyl, arylaminosulfonyl, amino wherein the nitrogen atom may be independently mono or di-substituted by C1-5 alkyl or aryl, halogen, hydroxy, oxo, carboxy and cyano;

or R_5 and R_9 together with the carbon they are attached form a carbocyclic ring selected from :



each carbocyclic ring being optionally benzofused and optionally substituted with one or more R_g;

R_g is selected from C1-5 alkyl, phenyl, C1-5 alkoxycarbonyl, aryloxycarbonyl, arylC1-3alkoxycarbonyl, carbamoyl wherein the nitrogen atom may be optionally mono or di-substituted with C1-5 alkyl, C3-6 cycloalkyl, phenyl, naphthyl or arylC1-3alkyl; halogen, hydroxy, carboxy and cyano;

R_6 is C3-6 cycloalkyloxycarbonyl, acetyl, C1-3alkylaminocarbonyl or C1-3alkoxycarbonyl; and

R_8 is hydrogen, C1-3 alkyl or C1-3 alkoxy.

12. The compound according claim 11 wherein:

R_1 is morpholin-4-yl, p-fluorophenyl or p-methoxyphenyl;

R_3 is a bond, methyl, ethyl, n-propyl, propenyl, butenyl, i-butenyl, C1-5 alkoxyC1-5 alkyl, C1-5 alkoxycarbonylC1-5 alkyl, C1-5 alkylthioC1-5 alkyl, C1-5 alkylsulfinylC1-5 alkyl, C1-5 alkylsulfonylC1-5 alkyl, aminoC1-5 alkyl, mono or di-alkylaminoC1-5 alkyl,

mono or di-alkylamidoC1-5 alkyl, cyclohexyl, heterocyclylC1-2 alkyl wherein the heterocyclic moiety is selected from pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, 8-aza-bicyclo[3.2.1]octane, silinane, piperazinyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydrothiopyranyl and indolyl, benzyl or naphthylmethyl wherein R_3 is optionally substituted by one or more R_c;

R_c is cyclohexyl, cyclopentyl, indanyl, bicyclo[2.2.1]heptanyl, bicyclo[2.2.2]octanyl, bicyclo[4.1.0]heptanyl, bicyclo[3.1.0]hexanyl, bicyclo[1.1.1]pentanyl, spiro[2.5] octanyl, spiro[3.5] nonyl, spiro[4.5] decanyl, cubanyl, 1,2,3,4-tetrahydronaphthyl, phenoxy, benzoyl, phenoxycarbonyl, benzoyloxy, phenylthio, fluoro or chloro;

R_9 is hydrogen, C1-5 alkyl, C1-5 alkylene, C1-5 alkoxyC1-5 alkyl, C1-5 alkoxycarbonylC1-5 alkyl, C1-5 alkylthioC1-5 alkyl, C1-5 alkylsulfinylC1-5 alkyl, C1-5 alkylsulfonylC1-5 alkyl, aminoC1-5 alkyl, mono or di-C1-5alkylaminoC1-5 alkyl, mono or di-C1-5 alkylamidoC1-5 alkyl, phenyl, furanyl, thienyl, thiazolyl, imidazolyl, pyridinyl, indolyl or cyano wherein R_9 is optionally substituted by one to two groups of the formula R_e;

R_e is selected from C1-3 alkyl, C3-6 cycloalkyl, phenyl, naphthyl, benzoyl, furanyl, thienyl, thiazolyl, imidazolyl, pyridinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, indolyl, halogen, hydroxy, oxo, carboxy and cyano, R_e may be further optionally substituted by one or more R_f;

R_f is selected from C1-3 alkyl, phenyl optionally substituted by one or more groups selected from halogen and methyl, heterocyclyl selected from piperidinyl, morpholinyl and piperazinyl; heteroaryl selected from furanyl, thienyl, pyrrolyl and pyridinyl, C1-3 alkoxy, aryloxy, benzoyl, benzyloxy, C1-5 alkoxycarbonyl, C1-5 alkanoyloxy, aroyloxy, carbamoyl wherein the nitrogen atom may be independently mono or di-substituted by C1-5 alkyl or phenyl, C1-5 alkanoylamino, aroylamino, C1-5 alkylthio wherein the

sulfur atom may be oxidized to a sulfoxide or sulfone, ureido wherein either nitrogen atom may be independently substituted by C1-5 alkyl or phenyl, C1-5 alkoxycarbonylamino, C1-5 alkylcarbamoyloxy, arylcarbamoyloxy, C1-3 alkylsulfonylamino, arylsulfonylamino, C1-3 alkylaminosulfonyl, arylaminosulfonyl, amino wherein the nitrogen atom may be independently mono or di-substituted by C1-3 alkyl or phenyl, halogen, hydroxy, oxo, nitro, carboxy and cyano;

R_7 is selected from C1-3 alkyl, phenyl, C1-3 alkoxycarbonyl, phenoxyoxycarbonyl, benzyloxy, carbamoyl wherein the nitrogen atom may be optionally mono or di-substituted with a group selected from C1-5 alkyl, phenyl and benzyl, halogen, hydroxy, carboxy and cyano;

R_6 is C3-6 cycloalkyloxycarbonyl, acetyl, ethylaminocarbonyl or ethoxycarbonyl; and

R_8 is hydrogen.

13. The compound according claim 12 wherein:

R_3 is methyl, ethyl, n-propyl, propenyl, butenyl, i-butenyl, C1-3 alkoxyC1-3 alkyl, C1-3 alkoxycarbonylC1-3 alkyl, C1-3 alkylthioC1-3 alkyl, C1-3 alkylsulfinylC1-3 alkyl, C1-3 alkylsulfonylC1-3 alkyl, aminoC1-3 alkyl, mono or di-C1-3 alkylaminoC1-3 alkyl, mono or di-C1-3 alkylamidoC1-3 alkyl, heterocyclylC1-2 alkyl wherein the heterocyclic moiety is selected from pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, 8-aza-bicyclo[3.2.1]octane, silinane, piperazinyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydrothiopyranyl and indolyl, benzyl or naphthylmethyl wherein R_3 is optionally substituted by one to two R_c;

R_c is methyl, cyclohexyl, cyclopentyl, indanyl, 1,2,3,4-tetrahydronaphthyl, spiro[2.5] octanyl, spiro[3.5] nonyl, spiro[4.5] decanyl, fluoro or chloro;

R_9 is hydrogen, C1-4 alkyl, C1-5 alkylene, C1-3 alkoxyC1-3 alkyl, C1-3 alkoxycarbonylC1-3 alkyl, C1-3 alkylthioC1-3 alkyl, C1-3 alkylsulfinylC1-3 alkyl, C1-3 alkylsulfonylC1-3 alkyl, aminoC1-3 alkyl, mono or di-C1-3 alkylaminoC1-3 alkyl, mono or di-C1-3 alkylamidoC1-3 alkyl, phenyl, furanyl, thienyl, thiazolyl, imidazolyl, pyridinyl, indolyl or cyano wherein R_9 is optionally substituted by one to two groups of the formula R_e;

R_e is selected from methyl, C3-6 cycloalkyl, phenyl, benzoyl, naphthyl, furanyl, thienyl, thiazolyl, imidazolyl, pyridinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, indolyl, halogen, hydroxy, carboxy and cyano, R_e may be further optionally substituted by one or more R_f;.

R_f is selected from C1-3 alkyl, phenyl or phenylsulfonyl each optionally substituted by one or more groups selected from halogen or methyl, C1-3 alkoxy, aryloxy, benzoyl, benzyloxy, C1-3 alkoxycarbonyl, carbamoyl wherein the nitrogen atom may be independently mono or di-substituted by C1-3 alkyl or phenyl, C1-5 alkanoylamino, aroylamino, amino wherein the nitrogen atom may be independently mono or di-substituted by C1-3 alkyl or phenyl, halogen, hydroxy, oxo, nitro, carboxy and cyano;

R_g is selected from C1-3 alkyl, phenyl, C1-3 alkoxycarbonyl, benzyloxy and carboxy.

14. The compound according to claim 1 and wherein:

R_1 is a bond, C1-4 alkyl, C1-4 alkoxy, cyclopropyl, cyclohexyl, phenoxy, naphthyloxy, phenyl, benzyl, naphthyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, furanyl, thienyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, indolyl, quinolinyl, benzofuranyl, benzthienyl, benzimidazolyl, benzthiazolyl, benzoxazolyl or amino; wherein R_1 is optionally substituted by one or more R_a;

R_a is methyl, ethyl, propyl, i-propyl, cyclopropyl, cyclohexyl, phenyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, thienyl, imidazolyl, methoxy, ethoxy, acetyl, acetoxy, phenoxy, naphthyloxy, benzyloxy, methoxycarbonyl, ethoxycarbonyl, phenoxycarbonyl, naphthyloxycarbonyl, benzoyloxy, carbamoyl wherein the nitrogen atom may be independently mono or di-substituted by methyl, ethyl, phenyl, naphthyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl or piperazinyl,
or R_a is acetylamino, benzoylamino, methylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, ethylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, phenylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, ureido wherein either nitrogen atom may be independently substituted by methyl, ethyl, phenyl, naphthyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl or piperazinyl,
or R_a is methoxycarbonylamino, ethoxycarbonylamino, phenoxycarbonylamino, C1-2 alkylcarbamoyloxy, phenylcarbamoyloxy, naphthylcarbamoyloxy, C1-2 alkylsulfonylamino, phenylsulfonylamino, naphthylsulfonylamino, C1-2 alkylaminosulfonyl, phenylaminosulfonyl, naphthylaminosulfonyl, amino wherein the nitrogen atom may be independently mono or di-substituted by methyl, ethyl, phenyl, naphthyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl or piperazinyl,
or R_a is halogen, hydroxy, oxo, carboxy, cyano, nitro, carboxamide, amidino or guanidino, R_a may be further optionally substituted by one or more R_b;

R_b is methyl, ethyl, cyclopropyl, cyclohexyl, phenyl, methoxy, ethoxy, phenoxy, benzyloxy, fluoro, chloro, bromo, hydroxy, oxo, carboxy, cyano, nitro or carboxamide;

R_2 is hydrogen or methyl;

R_3 is a bond, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, n-pentyl, propenyl, i-butenyl, cyclohexyl, benzyl or naphthylmethyl wherein R_3 is optionally substituted by one or more R_c;

R_c is methyl, ethyl, cyclohexyl, cyclopentyl, phenyl, naphthyl, bicyclo[3.1.0]hexanyl, bicyclo[1.1.1]pentanyl, cubanyl, furanyl, tetrahydropyranyl, thienyl, oxazolyl, thiazolyl, imidazolyl, pyrimidinyl, methoxy, ethoxy, phenoxy, acetyl, benzoyl, methoxycarbonyl, phenoxycarbonyl, acetoxy, benzoyloxy,
or R_c is acetylamino, benzoylamino, methylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, phenylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone,
or R_c is phenoxycarbonylamino, phenylcarbamoyloxy, phenylsulfonylamino, phenylaminosulfonyl, amino wherein the nitrogen atom may be independently mono or di-substituted by methyl or phenyl,
or R_c is chloro, fluoro, hydroxy, oxo, carboxy or cyano;

R_2 and R_3 together with the carbon they are attached optionally form a ring selected from cyclopentyl, cyclohexyl, cycloheptyl, tetrahydropyranyl, tetrahydrothiopyranyl, tetrahydrofuranyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl or tetrahydrothiophenyl;

R_4 is hydrogen;
R_5 is hydrogen or C1-3alkyl;

R_9 is hydrogen, C1-12 alkyl wherein one or more carbon atoms are optionally replaced by O, S or N, phenyl or cyano, wherein R_9 is optionally substituted by one or more R_e;

R_e is selected from C1-3 alkyl, C3-6 cycloalkyl, phenyl, naphthyl, furanyl, thienyl, thiazolyl, imidazolyl, pyridinyl, indolyl, halogen, hydroxy, oxo, carboxy and cyano, R_e may be further optionally substituted by one or more R_f;

R_f is selected from C1-3 alkyl, phenyl optionally substituted by one or more groups selected from halogen and methyl, heterocyclyl selected from piperidinyl, morpholinyl and piperazinyl; heteroaryl selected from furanyl, thienyl, pyrrolyl and pyridinyl, C1-3 alkoxy, aryloxy, benzyloxy, C1-5 alkoxycarbonyl, C1-5 alkanoyloxy, aroyloxy, carbamoyl wherein the nitrogen atom may be independently mono or di-substituted by C1-5 alkyl or phenyl, C1-5 alkanoylamino, aroylamino, C1-5 alkylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, ureido wherein either nitrogen atom may be independently substituted by C1-5 alkyl or phenyl, C1-5 alkoxycarbonylamino, C1-5 alkylcarbamoyloxy, arylcarbamoyloxy, C1-3 alkylsulfonylamino, arylsulfonylamino, C1-3 alkylaminosulfonyl, arylaminosulfonyl, amino wherein the nitrogen atom may be independently mono or di-substituted by C1-3 alkyl or phenyl, halogen, hydroxy, oxo, carboxy and cyano;

or R_5 and R_9 together with the carbon they are attached form a carbocyclic ring of 3 to 5 carbon atoms, the carbocyclic ring being optionally substituted with one or more R_g;

R_g is selected from C1-3 alkyl, phenyl, C1-3 alkoxycarbonyl, benzyloxy, carbamoyl wherein the nitrogen atom may be optionally mono or di-substituted with a group selected from C1-5 alkyl, phenyl and benzyl, halogen, hydroxy, carboxy and cyano.

15. The compound according to claim 14 and wherein:

R_1 is a bond, methyl, ethyl, n-propyl, i-propyl, methoxy, ethoxy, benzyloxy, cyclopropyl, cyclohexyl, phenoxy, naphthyloxy, phenyl, benzyl, naphthyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, furanyl, thienyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, indolyl, quinolinyl,

benzofuranyl, benzthienyl, benzimidazolyl, benzthiazolyl, benzoxazolyl or amino; wherein R_1 is optionally substituted by one or more R_a;

R_a is methyl, cyclopropyl, phenyl, halogen, hydroxy, oxo, carboxy, cyano, nitro or carboxamide;

R_3 is a bond, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, n-pentyl, propenyl, i-butenyl, benzyl or naphthylmethyl wherein R_3 is optionally substituted by one or more R_c;

R_c is methyl, ethyl, cyclohexyl, cyclopentyl, phenyl, furanyl, tetrahydropyranyl, thienyl, oxazolyl, thiazolyl, methoxy, phenoxy, acetyl, benzoyl, methoxycarbonyl, or R_c is acetylamino, benzoylamino, methylthio, amino wherein the nitrogen atom may be independently mono or di-substituted by methyl, or R_c is fluoro or oxo;

R_2 and R_3 together with the carbon they are attached optionally form a ring selected from cyclopentyl, cyclohexyl, cycloheptyl, tetrahydropyranyl, tetrahydrothiopyranyl, tetrahydrofuranyl, pyrrolidinyl or piperidinyl;

R_5 is hydrogen or methyl;

R_9 is hydrogen, C1-12 alkyl wherein one or more carbon atoms are optionally replaced by O, S or N, phenyl or cyano wherein R_9 is optionally substituted by one or more groups of the formula R_e;

R_e is selected from methyl, C3-6 cycloalkyl, phenyl, naphthyl, furanyl, thienyl, thiazolyl, imidazolyl, pyridinyl, indolyl, halogen, hydroxy, oxo, carboxy and cyano, R_e may be further optionally substituted by one or more R_f.

R_f is selected from C1-3 alkyl, phenyl optionally substituted by one or more groups selected from halogen or methyl, C1-3 alkoxy, aryloxy, benzyloxy, C1-3 alkoxycarbonyl, carbamoyl wherein the nitrogen atom may be independently mono or di-substituted by C1-3 alkyl or phenyl, C1-5 alkanoylamino, aroylamino, amino wherein the nitrogen atom may be independently mono or di-substituted by C1-3 alkyl or phenyl, halogen, hydroxy, oxo, carboxy and cyano;

or R_5 and R_9 together with the carbon they are attached form a carbocyclic ring of 3 to 5 carbon atoms, the carbocyclic ring being optionally substituted with one or more R_g;

R_g is selected from C1-3 alkyl, phenyl, C1-3 alkoxycarbonyl, benzyloxy and carboxy.

16. The compound according to claim 15 and wherein:

R_1 is methoxy, benzyloxy, cyclohexyl, phenoxy, naphthyloxy, phenyl, benzyl, naphthyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, furanyl, thienyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, quinolinyl, benzofuranyl, benzthienyl, benzimidazolyl, benzthiazolyl, benzoxazolyl or amino; wherein R_1 is optionally substituted by one or more R_a;

R_a is methyl, phenyl, fluoro, chloro, hydroxy, oxo, carboxy or carboxamide;

R_3 is a bond, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, n-pentyl, propenyl, i-butenyl or benzyl wherein R_3 is optionally substituted by one or more R_c;

R_c is methyl, ethyl, cyclohexyl, cyclopentyl, phenyl, furanyl, tetrahydropyranyl, thienyl, oxazolyl, thiazolyl, methoxy, phenoxy, acetyl, benzoyl, methoxycarbonyl, acetylamino, methylthio or fluoro;

R_2 and R_3 together with the carbon they are attached optionally form a ring selected from cyclopentyl, cyclohexyl, cycloheptyl, tetrahydropyranyl, tetrahydrothiopyranyl or tetrahydrofuranyl;

R_9 is hydrogen, C1-5 alkyl, C1-5 alkylene, C1-5 alkoxyC1-5 alkyl, C1-5 alkoxycarbonylC1-5 alkyl, C1-5 alkylthioC1-5 alkyl, C1-5 alkylthiosulfoneC1-5 alkyl, C1-5 alkylthiosulfonylC1-5 alkyl, aminoC1-5 alkyl, mono or di-C1-5alkylaminoC1-5 alkyl, mono or di-C1-5 alkylamidoC1-5 alkyl or phenyl, wherein R_9 is optionally substituted by one or more R_e;

R_e is selected from C3-6 cycloalkyl, phenyl, naphthyl, thienyl, imidazolyl, pyridinyl, indolyl, halogen, hydroxy, carboxy and cyano, R_e may be further optionally substituted by one or more R_f;

R_f is selected from methyl, phenyl optionally substituted by one or more groups selected from halogen or methyl, methoxy, phenoxy, benzyloxy, methoxycarbonyl, amino wherein the nitrogen atom may be independently mono or di-substituted by C1-3 alkyl or phenyl, halogen, hydroxy and carboxy;

or R_5 and R_9 together with the carbon they are attached form a carbocyclic ring of 3 to 5 carbon atoms, the carbocyclic ring being optionally substituted with one or more R_g;

R_g is selected from phenyl, methoxycarbonyl, benzyloxycarbonyl and carboxy.

17. The compound according to claim 16 and wherein:

R_1 is benzyloxy, phenoxy, naphthyloxy, phenyl, naphthyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, pyridinyl, indolyl, quinolinyl, benzofuranyl, benzthienyl, benzimidazolyl, benzthiazolyl, benzoxazolyl or phenylamino;

R_3 is n-propyl, i-butyl, propenyl, i-butenyl or 2,2-dimethylpropyl;

R_2 and R_3 together with the carbon they are attached optionally form a ring selected from cyclopentyl, cyclohexyl, or cycloheptyl;

R_5 is hydrogen;

R_e is selected from C5-6 cycloalkyl, phenyl, naphthyl, thienyl, indolyl, halogen, hydroxy, carboxy and cyano, R_f may be further optionally substituted by one or more R_f;

R_f is selected from methyl, phenyl optionally substituted by halogen, methoxy, phenoxy, benzyloxy, methoxycarbonyl, halogen, hydroxy and carboxy;

or R_5 and R_9 together with the carbon they are attached form a carbocyclic ring of 3 carbon atoms, the carbocyclic ring being optionally substituted with one or more R_g;

R_g is phenyl.

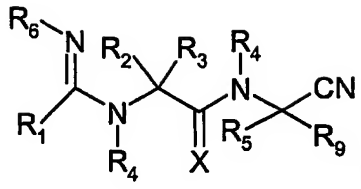
18. The compound according to claim 17 and wherein:

R_e is selected from C5-6 cycloalkyl, phenyl, naphthyl, indolyl, halogen and carboxy, R_f may be further optionally substituted by one or more R_f;

R_f is selected from methyl, methoxy, methoxycarbonyl, halogen and hydroxy, and

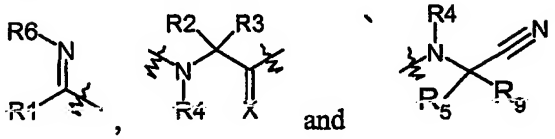
R_5 and R_9 together with the carbon they are attached form a carbocyclic ring of 3 carbon atoms, the carbocyclic ring being optionally substituted with one or more R_g.

19. A compound formula (Ia)

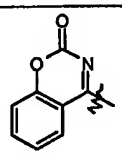
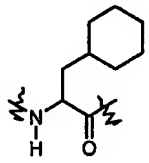
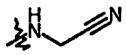
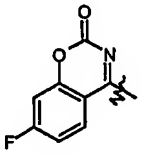
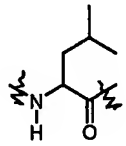
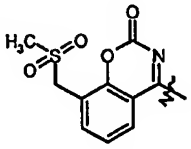
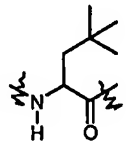
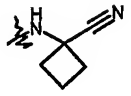
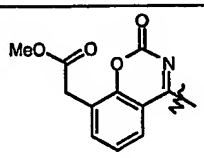
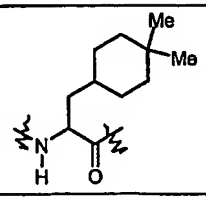
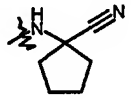


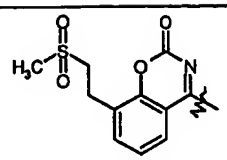
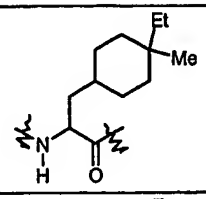
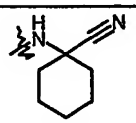
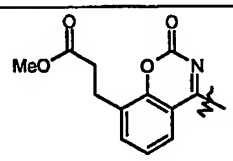
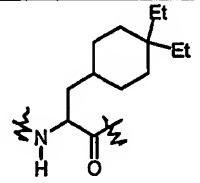
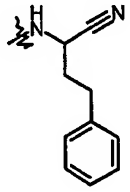
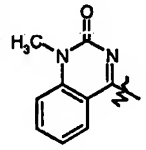
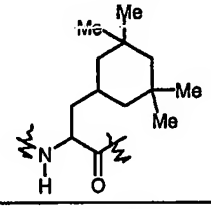
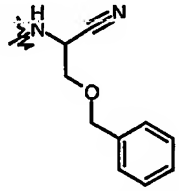
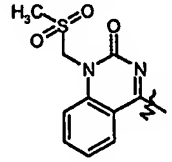
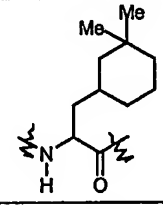
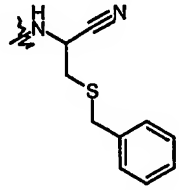
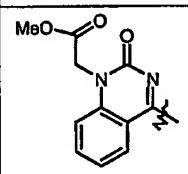
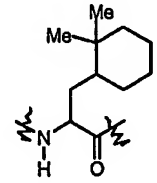
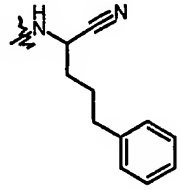
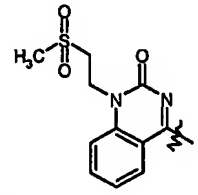
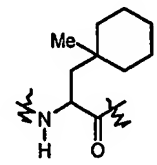
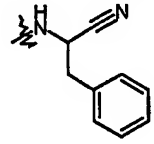
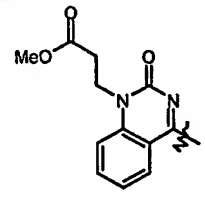
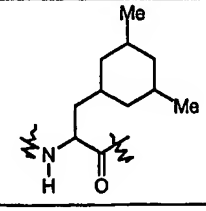
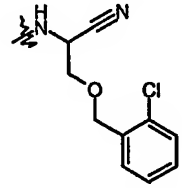
(Ia)

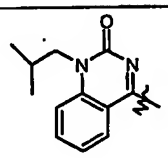
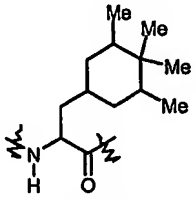
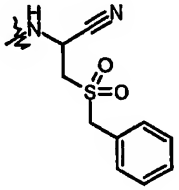
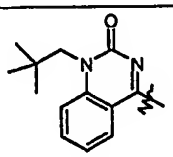
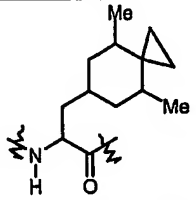
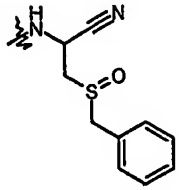
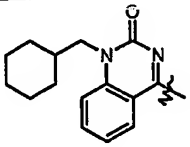
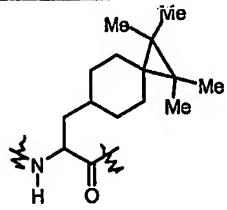
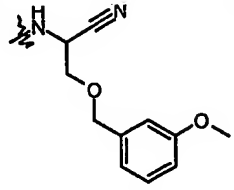
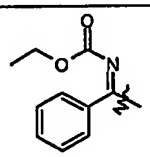
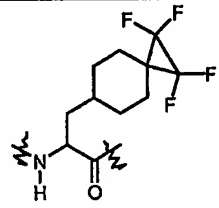
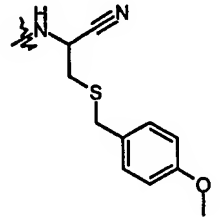
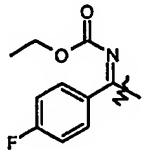
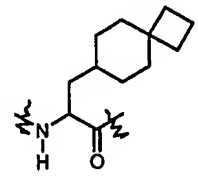
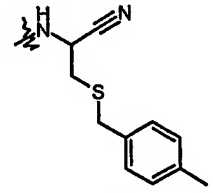
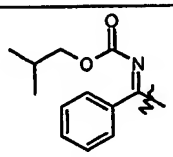
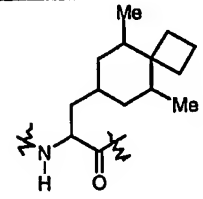
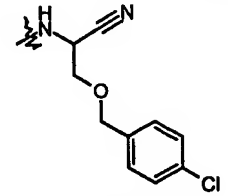
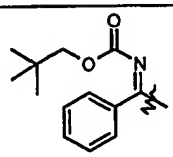
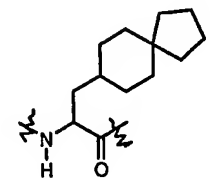
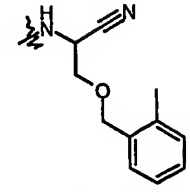
wherein for the formula (Ia), the components

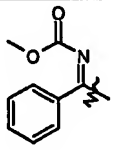
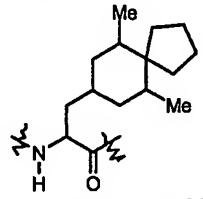
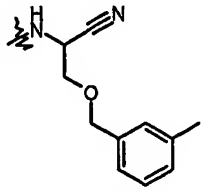
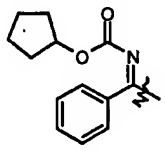
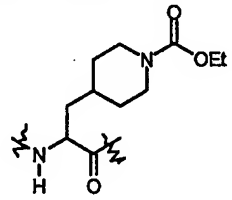
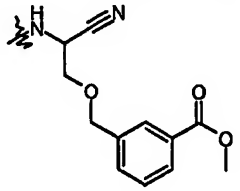
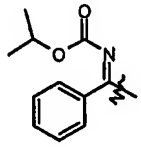
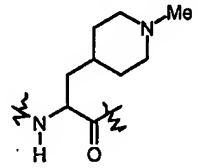
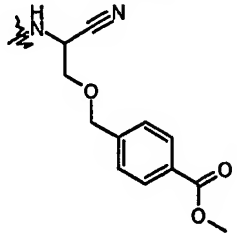
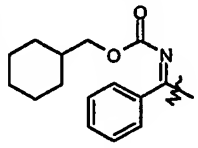
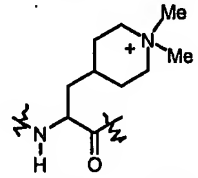
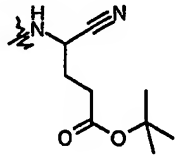
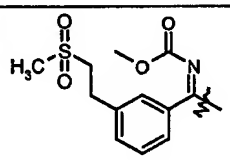
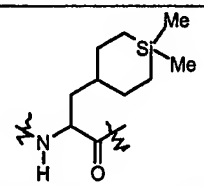
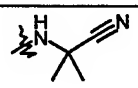
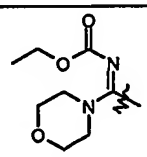
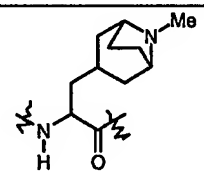
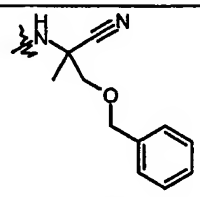
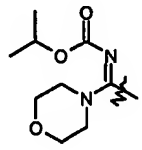
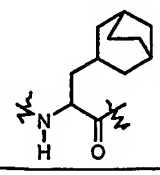
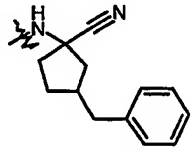


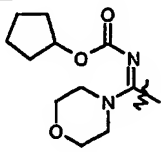
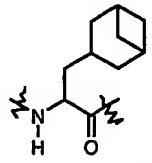
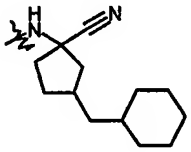
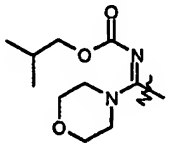
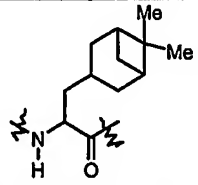
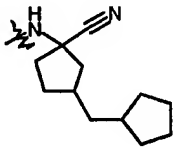
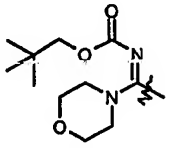
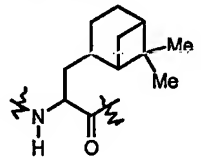
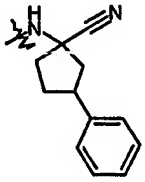
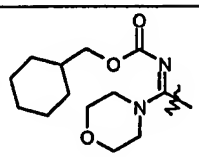
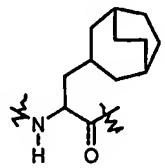
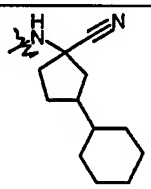
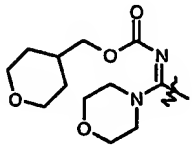
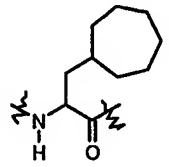
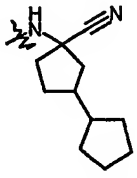
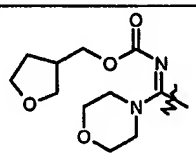
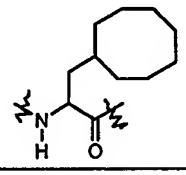
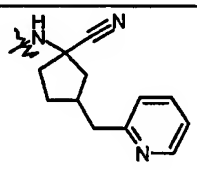
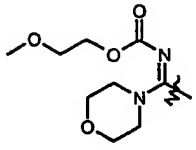
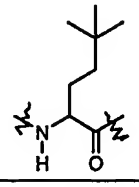
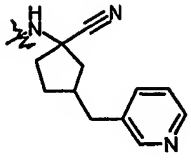
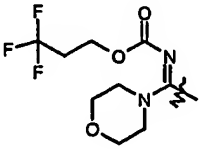
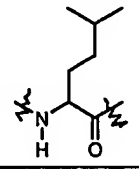
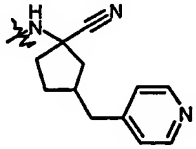
are chosen from any combination of A, B and C as follows:

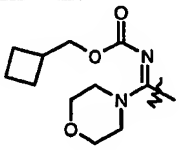
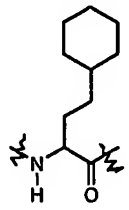
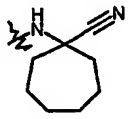
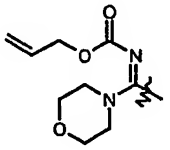
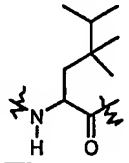
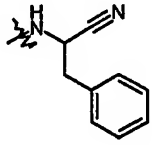
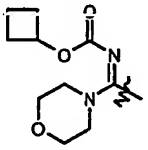
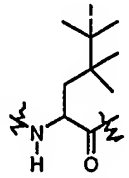
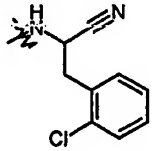
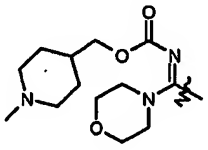
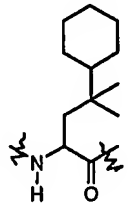
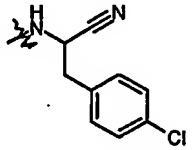
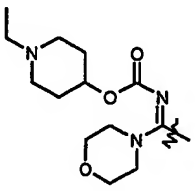
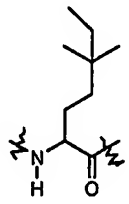
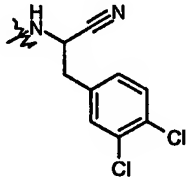
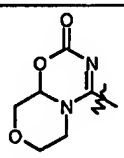
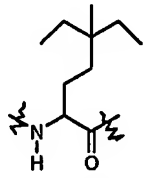
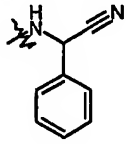
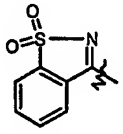
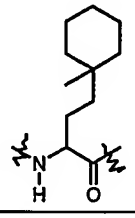
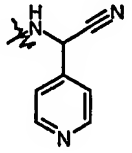
A		B		C	
A1		B1		C1	
A2		B2		C2	
A3		B3		C3	
A4		B4		C4	

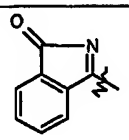
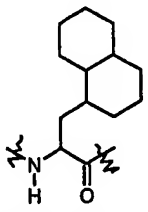
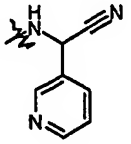
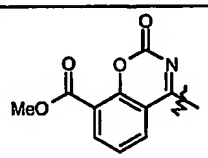
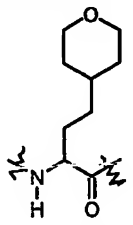
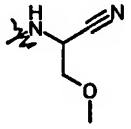
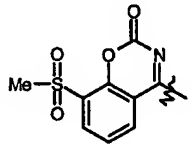
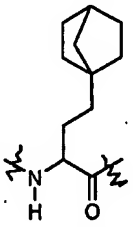
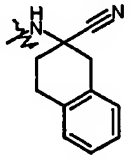
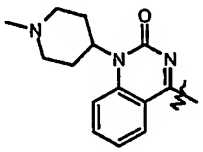
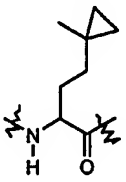
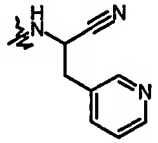
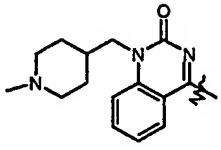
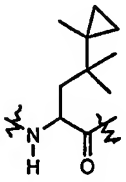
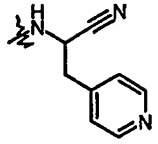
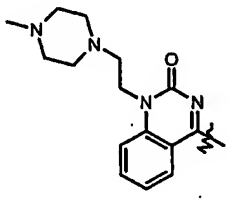
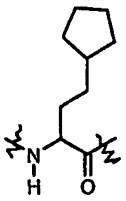
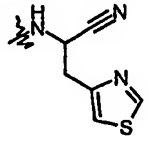
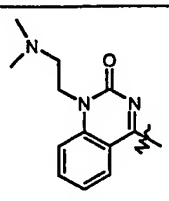
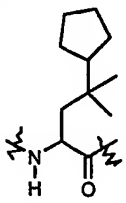
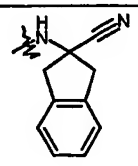
A5		B5		C5	
A6		B6		C6	
A7		B7		C7	
A8		B8		C8	
A9		B9		C9	
A10		B10		C10	
A11		B11		C11	

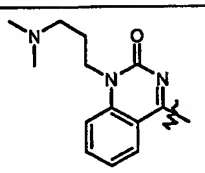
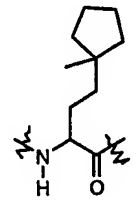
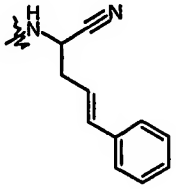
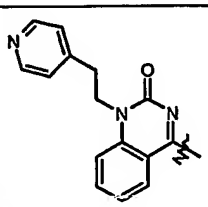
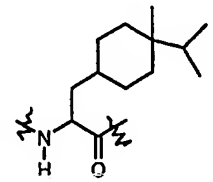
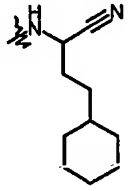
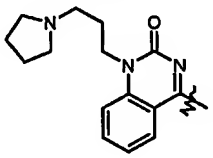
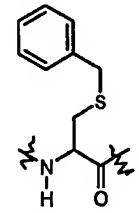
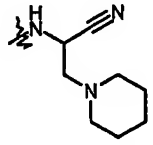
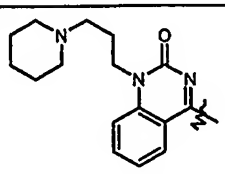
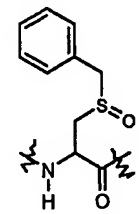
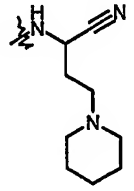
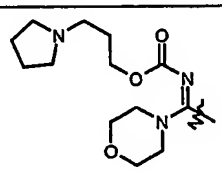
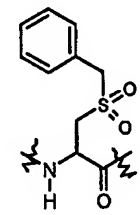
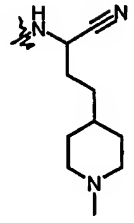
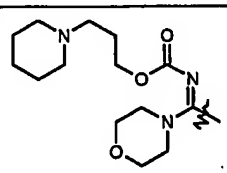
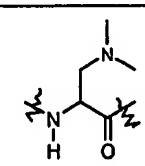
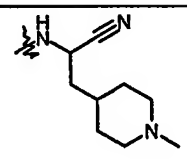
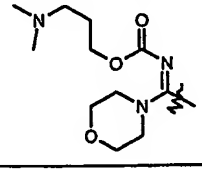
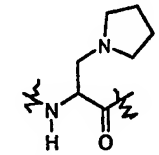
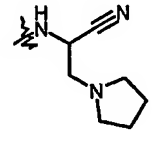
A12		B12		C12	
A13		B13		C13	
A14		B14		C14	
A15		B15		C15	
A16		B16		C16	
A17		B17		C17	
A18		B18		C18	

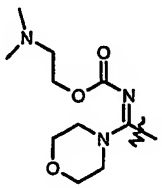
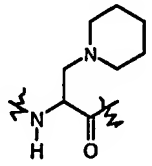
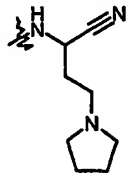
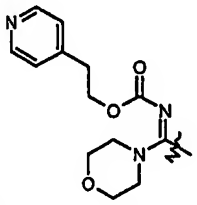
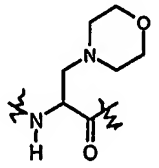
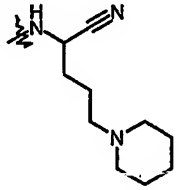
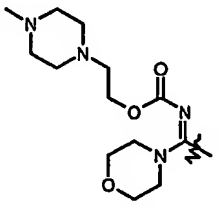
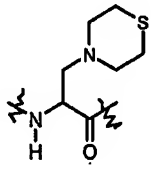
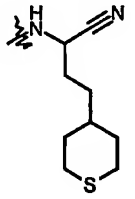
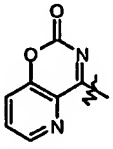
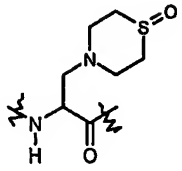
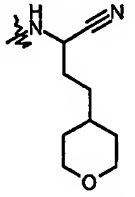
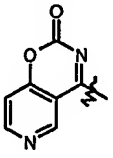
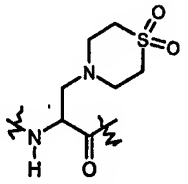
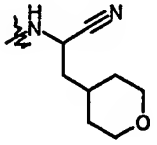
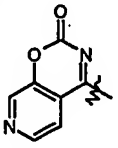
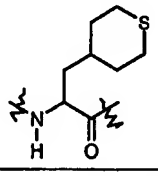
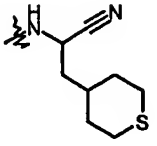
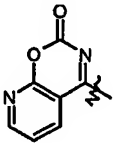
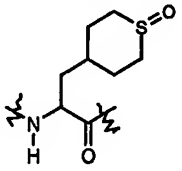
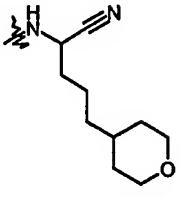
A19		B19		C19	
A20		B20		C20	
A21		B21		C21	
A22		B22		C22	
A23		B23		C23	
A24		B24		C24	
A25		B25		C25	

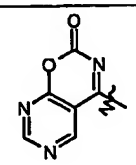
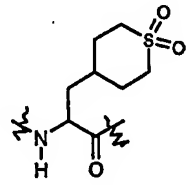
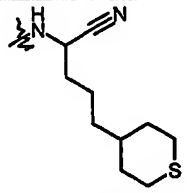
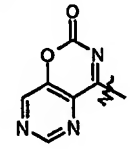
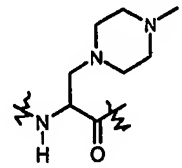
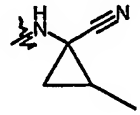
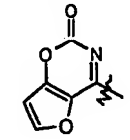
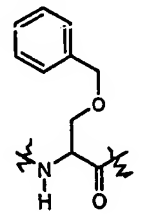
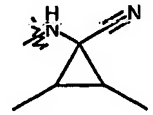
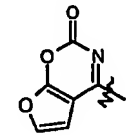
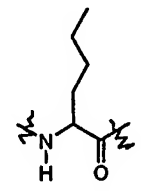
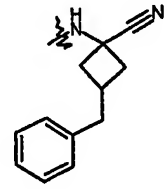
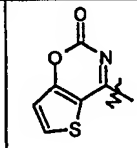
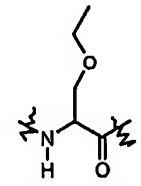
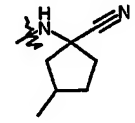
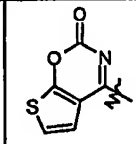
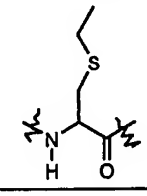
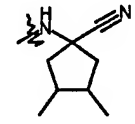
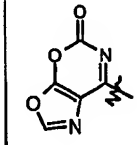
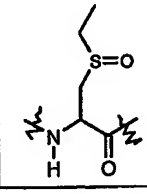
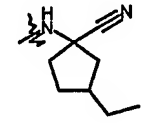
A26		B26		C26	
A27		B27		C27	
A28		B28		C28	
A29		B29		C29	
A30		B30		C30	
A31		B31		C31	
A32		B32		C32	
A33		B33		C33	

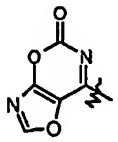
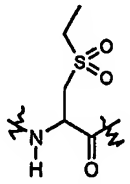
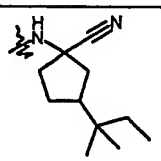
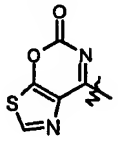
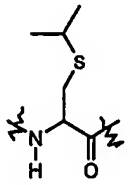
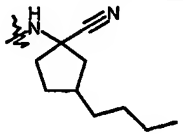
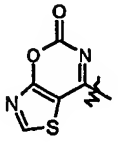
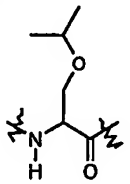
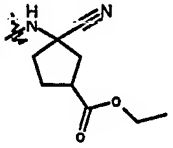
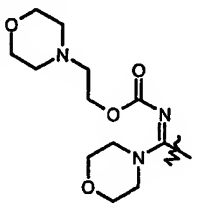
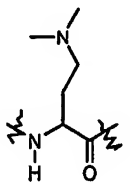
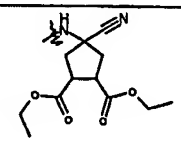
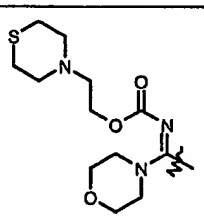
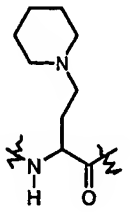
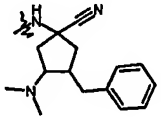
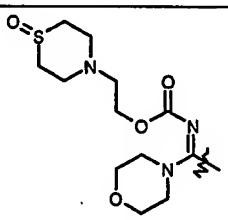
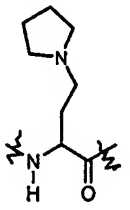
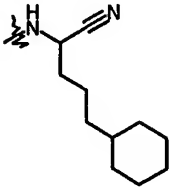
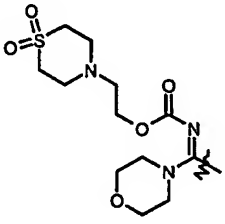
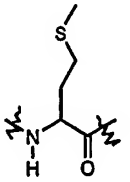
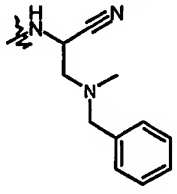
A34		B34		C34	
A35		B35		C35	
A36		B35		C36	
A37		B37		C37	
A38		B38		C38	
A39		B39		C39	
A40		B40		C40	

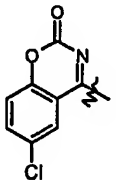
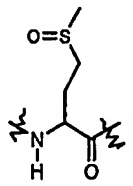
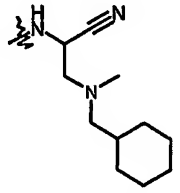
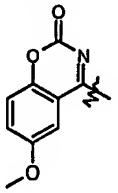
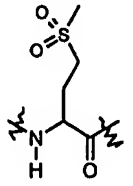
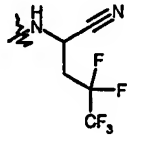
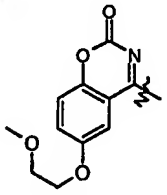
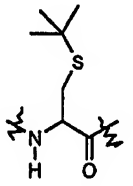
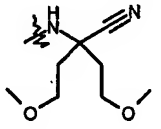
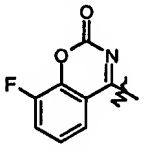
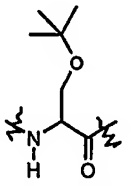
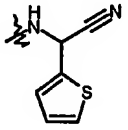
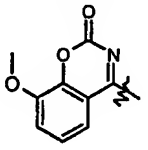
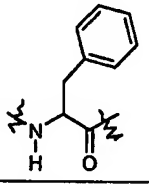
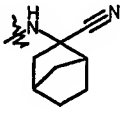
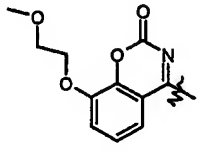
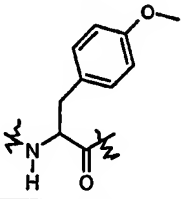
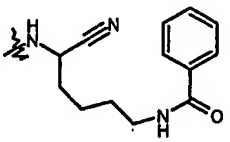
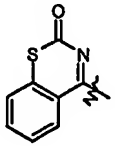
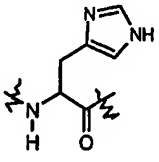
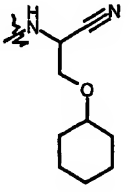
A41		B41		C41	
A42		B42		C42	
A43		B43		C43	
A44		B44		C44	
A45		B45		C45	
A46		B46		C46	
A47		B47		C47	

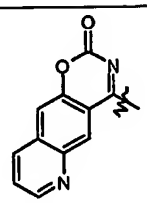
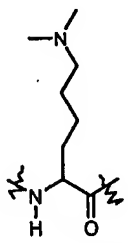
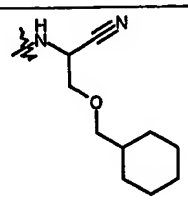
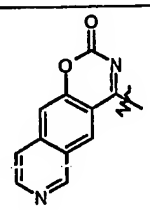
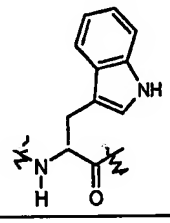
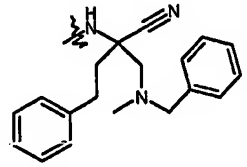
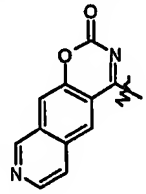
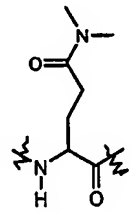
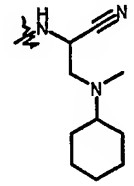
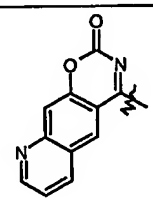
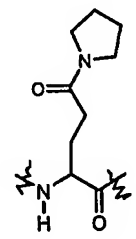
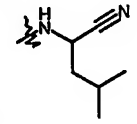
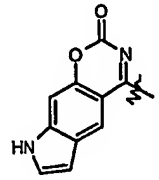
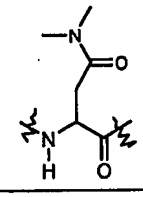
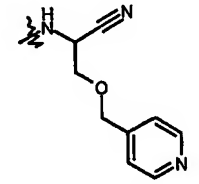
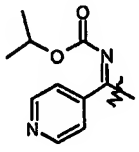
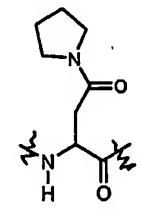
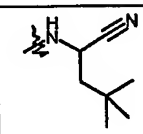
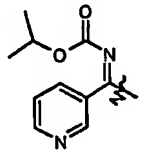
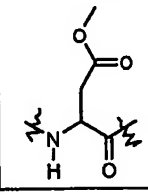
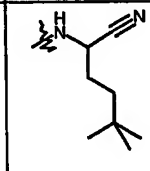
A48		B48		C48	
A49		B49		C49	
A50		B50		C50	
A51		B51		C51	
A52		B52		C52	
A53		B53		C53	
A54		B54		C54	

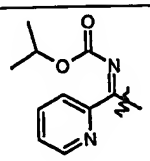
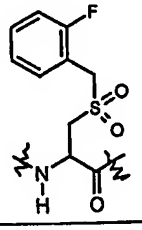
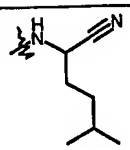
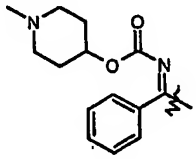
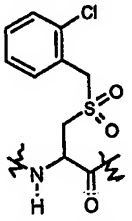
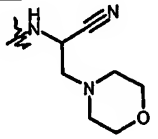
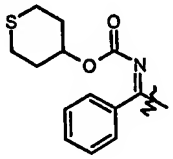
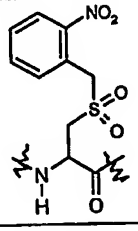
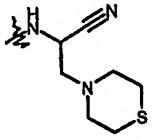
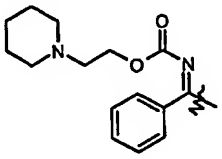
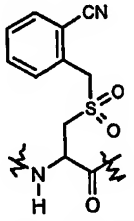
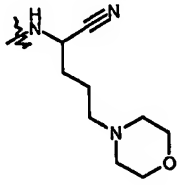
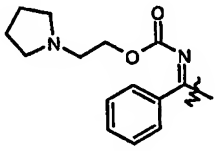
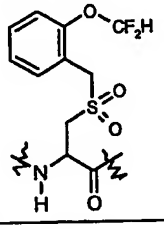
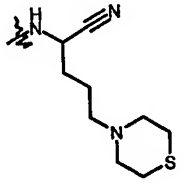
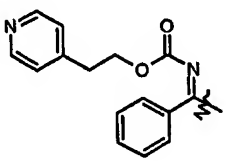
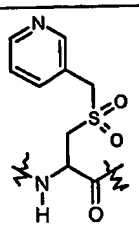
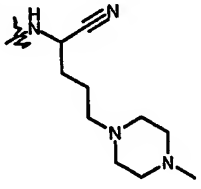
A55		B55		C55	
A56		B56		C56	
A57		B57		C57	
A58		B58		C58	
A59		B59		C59	
A60		B60		C60	
A61		B61		C61	

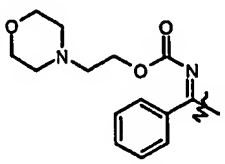
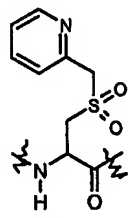
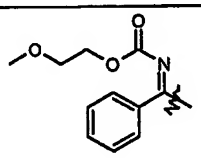
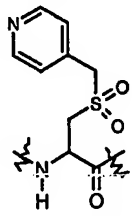
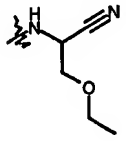
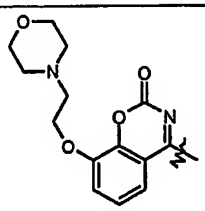
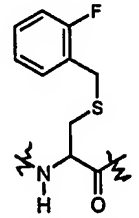
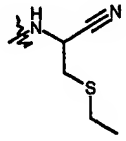
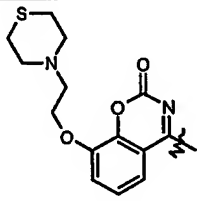
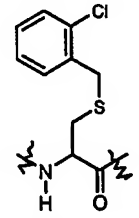
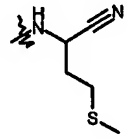
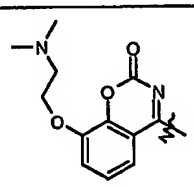
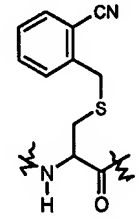
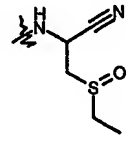
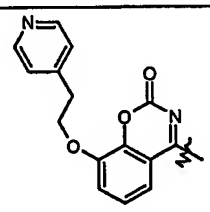
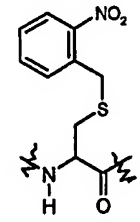
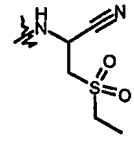
A62		B62		C62	
A63		B63		C63	
A64		B64		C64	
A65		B65		C65	
A66		B66		C66	
A67		B67		C67	
A68		B68		C68	

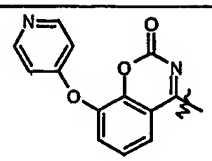
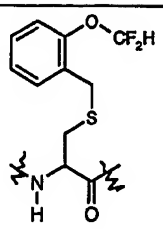
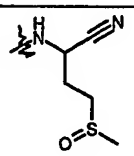
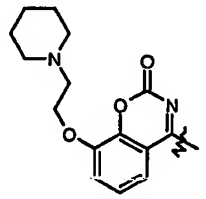
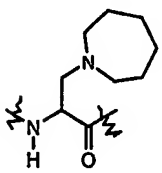
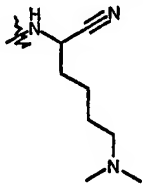
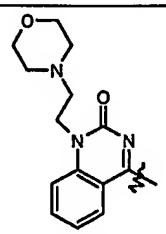
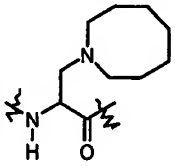
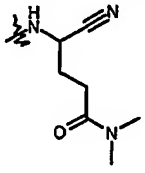
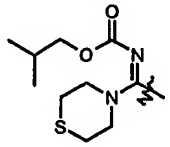
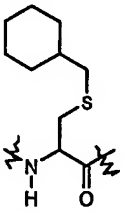
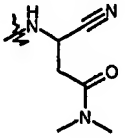
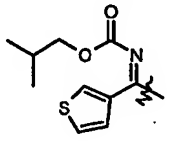
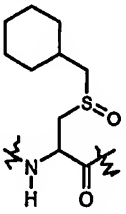
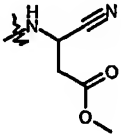
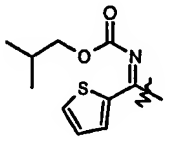
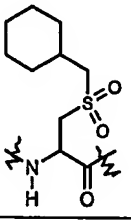
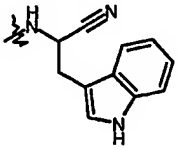
A69		B69		C69	
A70		B70		C70	
A71		B71		C71	
A72		B72		C72	
A73		B73		C73	
A74		B74		C74	
A75		B75		C75	

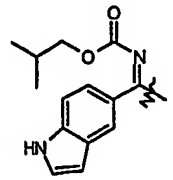
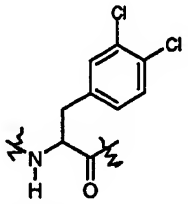
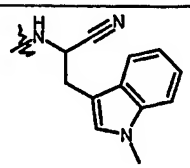
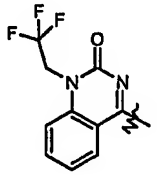
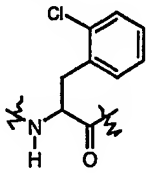
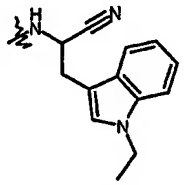
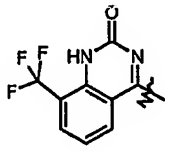
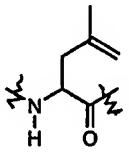
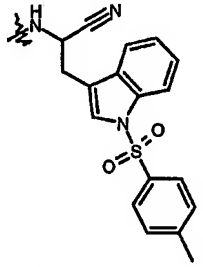
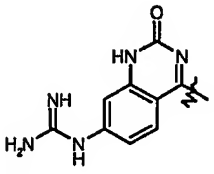
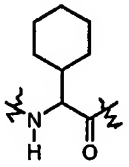
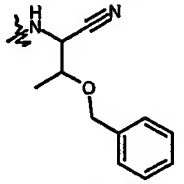
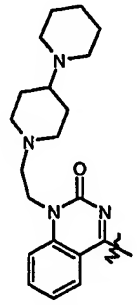
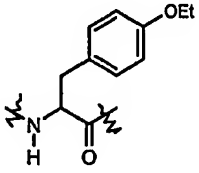
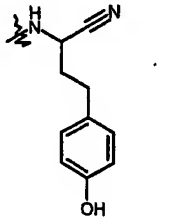
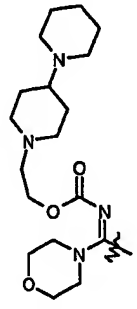
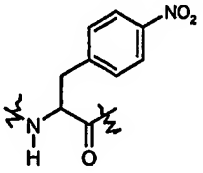
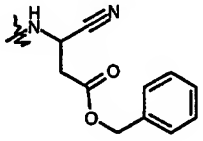
A76		B76		C76	
A77		B77		C77	
A78		B78		C78	
A79		B79		C79	
A80		B80		C80	
A81		B81		C81	
A82		B82		C82	

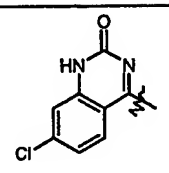
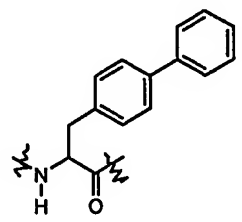
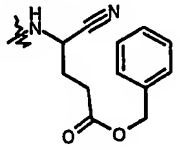
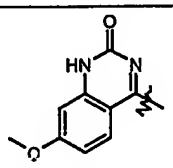
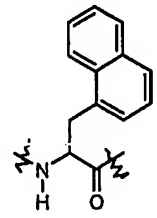
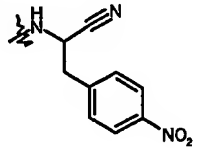
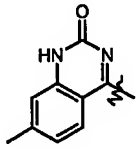
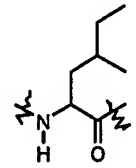
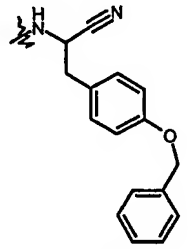
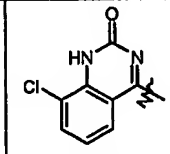
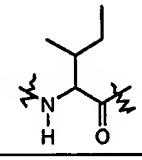
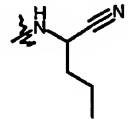
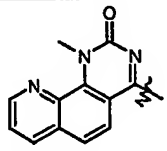
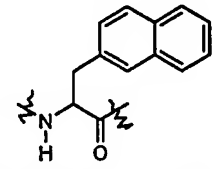
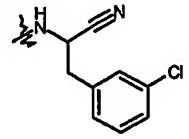
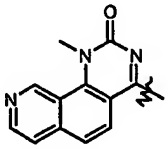
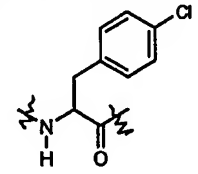
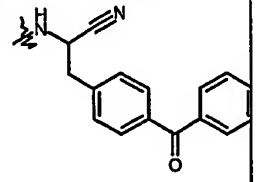
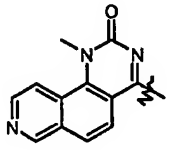
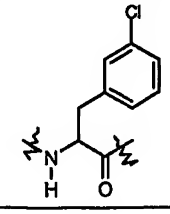
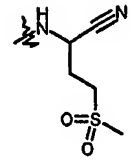
A83		B83		C83	
A84		B84		C84	
A85		B85		C85	
A86		B86		C86	
A87		B87		C87	
A88		B88		C88	
A89		B89		C89	

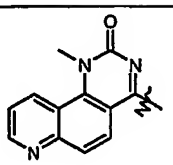
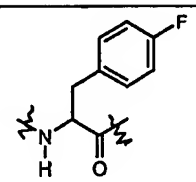
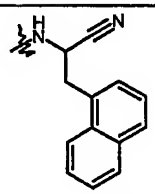
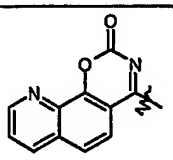
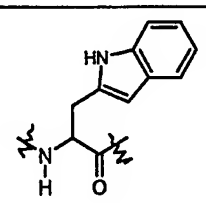
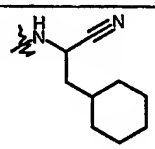
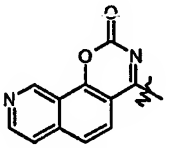
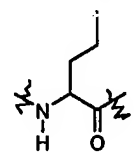
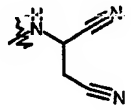
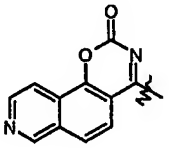
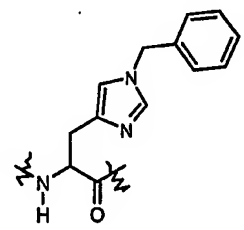
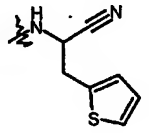
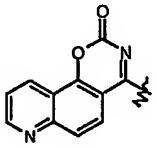
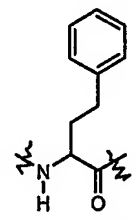
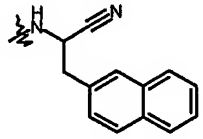
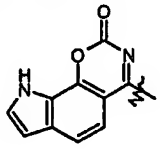
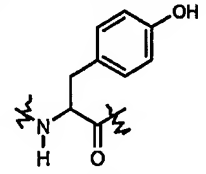
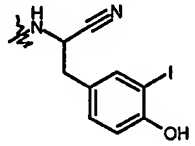
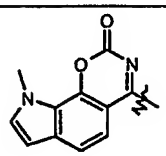
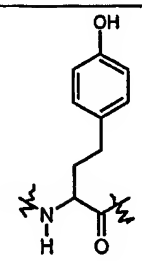
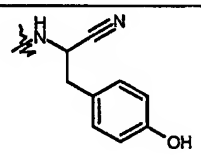
A90		B90		C90	
A91		B91		C91	
A92		B92		C92	
A93		B93		C93	
A94		B94		C94	
A95		B95		C95	

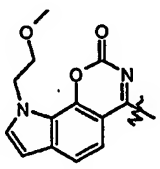
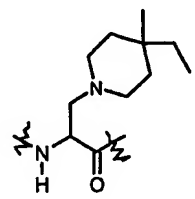
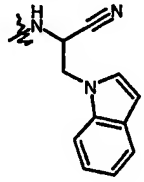
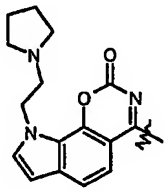
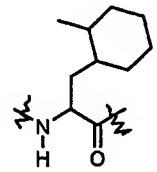
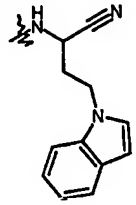
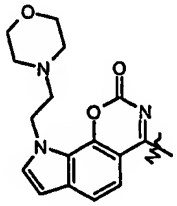
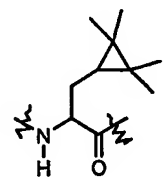
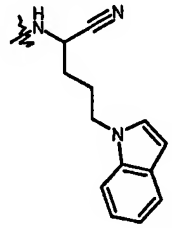
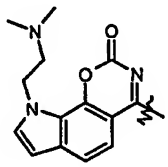
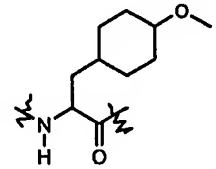
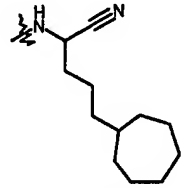
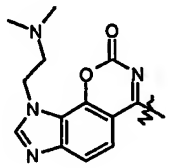
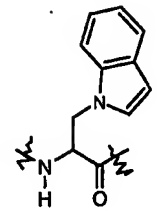
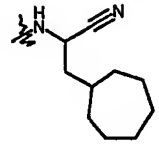
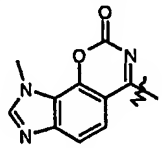
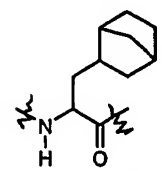
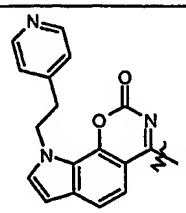
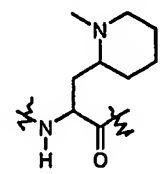
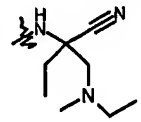
A96		B96		C96	
A97		B97		C97	
A98		B98		C98	
A99		B99		C99	
A100		B100		C100	
A101		B101		C101	

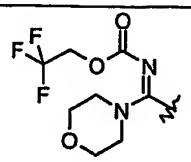
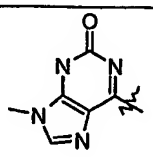
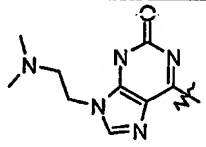
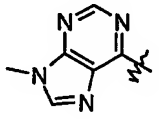
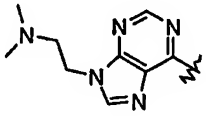
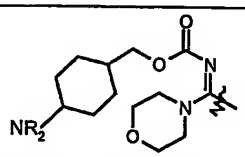
A102		B102		C102	
A103		B103		C103	
A104		B104		C104	
A105		B105		C105	
A106		B106		C106	
A107		B107		C107	

A108		B108		C108	
A109		B109		C109	
A110		B110		C110	
A111		B111		C111	
A112		B112		C112	
A113		B113		C113	

A114		B114		C114	
A115		B115		C115	
A116		B116		C116	
A117		B117		C117	
A118		B118		C118	
A119		B119		C119	
A120		B120		C120	

A121		B121		C121	
A122		B122		C122	
A123		B123		C123	
A124		B124		C124	
A125		B125		C125	
A126		B126		C126	
A127		B127		C127	

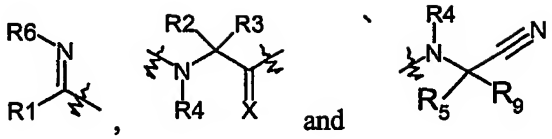
A128		B128		C128	
A129		B129		C129	
A130		B130		C130	
A131		B131		C131	
A132		B132		C132	
A133		B133		C133	
A134		B134		C134	

A135					
A136					
A137					
A138					
A139					
A140	 R is hydrogen or alkyl				

or the pharmaceutically acceptable salts, esters, tautomers, individual isomers and mixtures of isomers thereof.

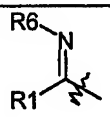
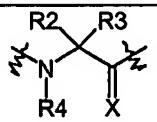
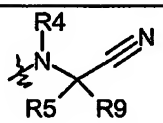
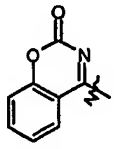
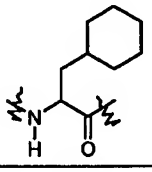
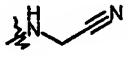
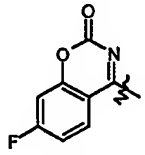
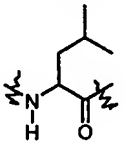
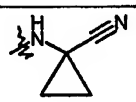
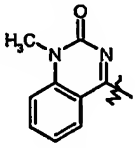
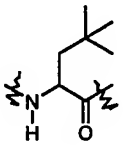
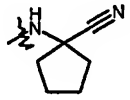
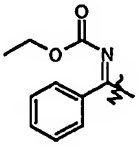
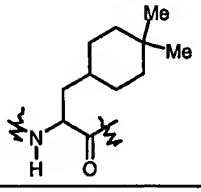
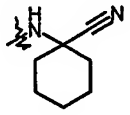
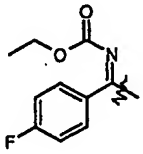
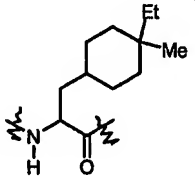
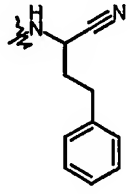
20. The compound of the formula (Ia) according to claim 19 and wherein:

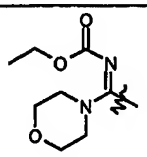
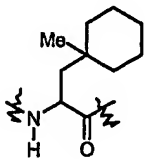
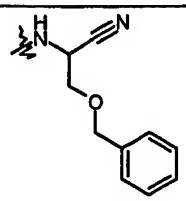
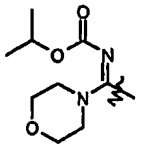
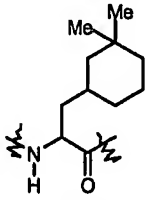
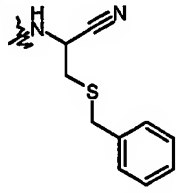
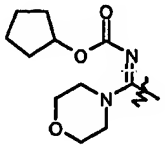
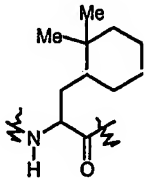
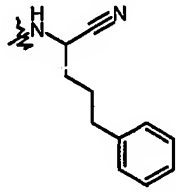
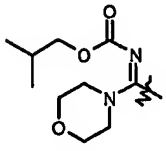
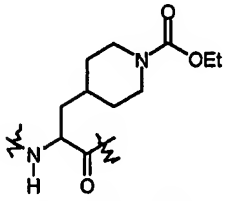
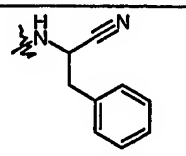
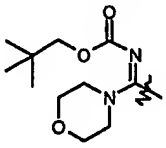
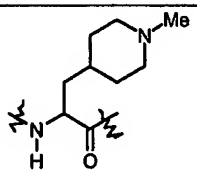
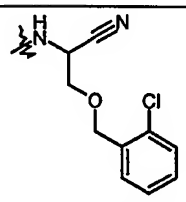
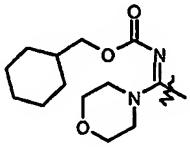
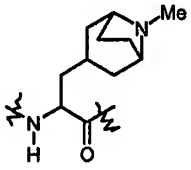
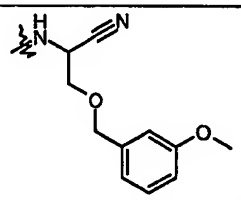
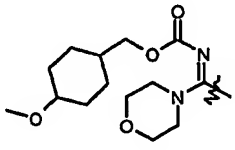
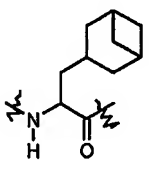
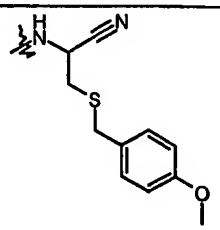
for the formula (Ia), the components

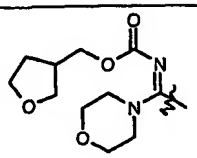
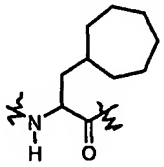
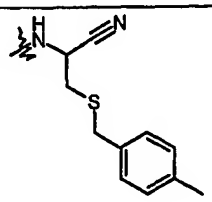
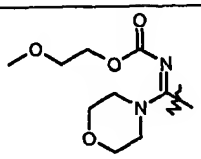
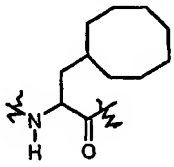
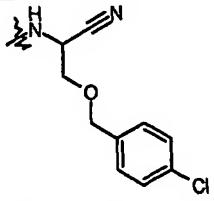
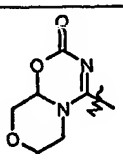
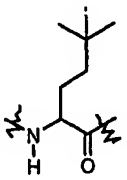
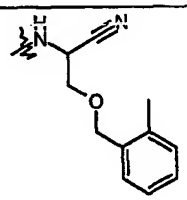
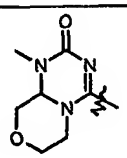
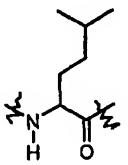
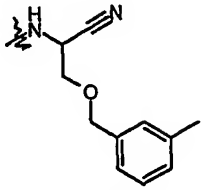
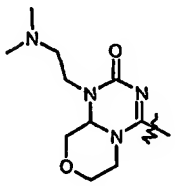
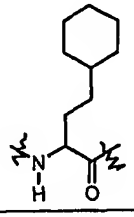
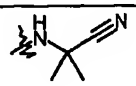
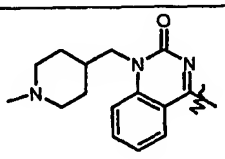
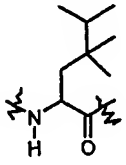
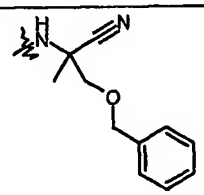
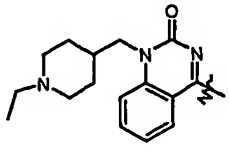
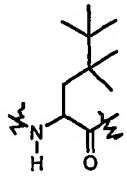
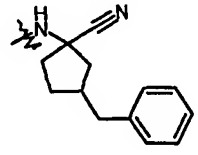


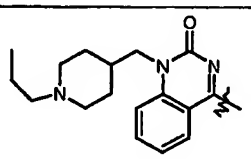
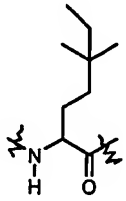
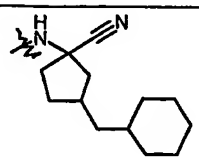
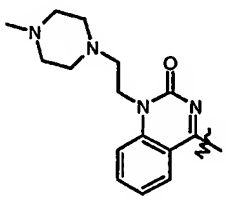
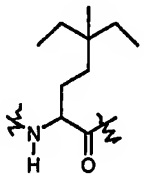
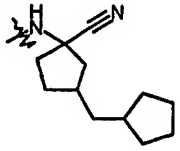
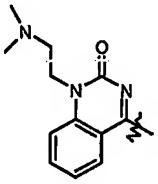
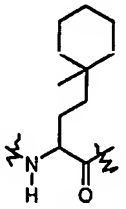
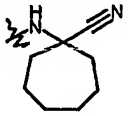
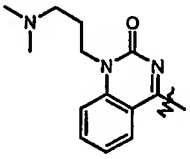
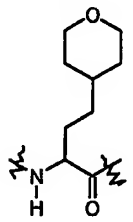
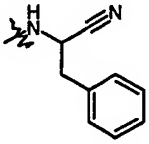
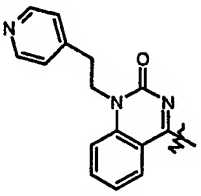
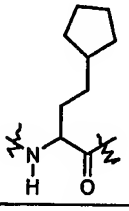
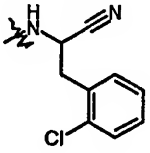
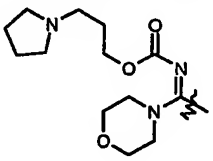
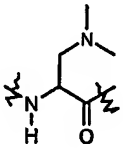
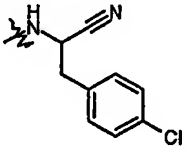
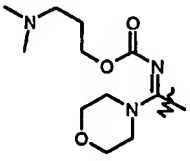
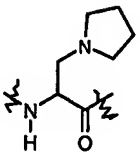
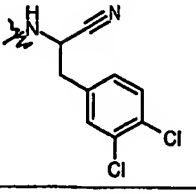
and

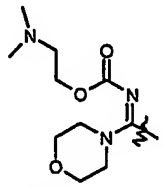
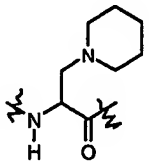
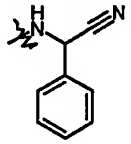
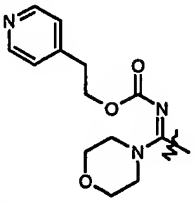
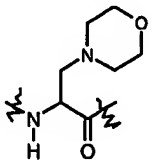
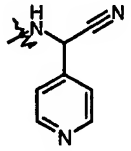
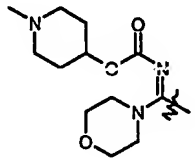
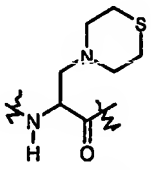
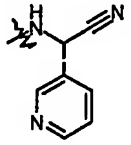
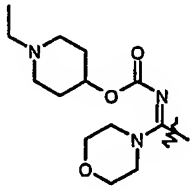
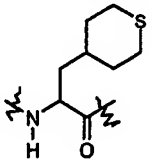
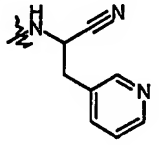
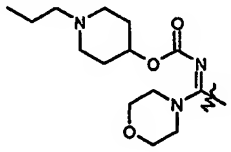
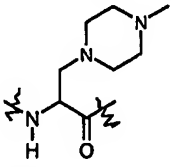
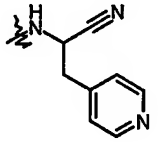
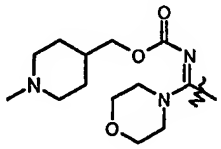
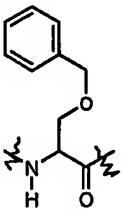
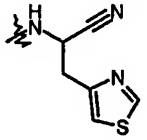
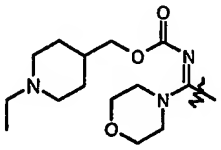
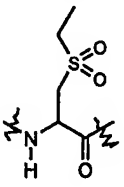
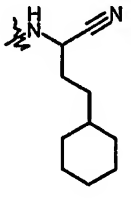
are chosen from any combination of A, B and C as follows:

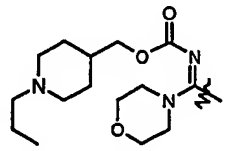
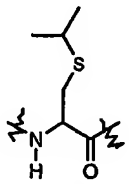
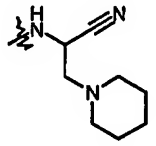
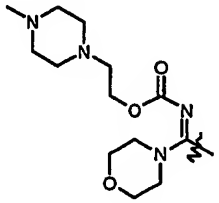
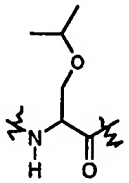
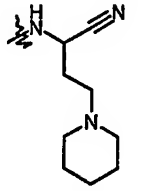
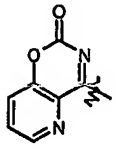
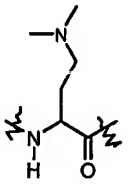
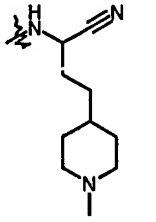
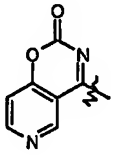
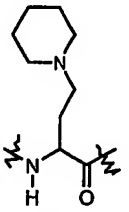
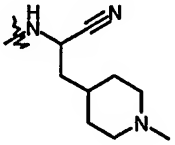
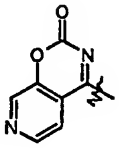
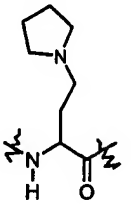
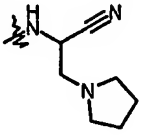
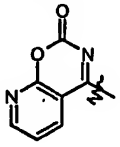
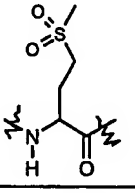
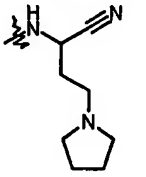
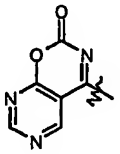
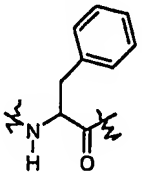
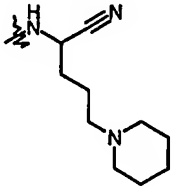
A		B		C	
A1		B1		C1	
A2		B2		C2	
A3		B3		C3	
A4		B4		C4	
A5		B5		C5	

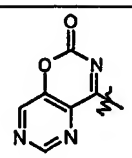
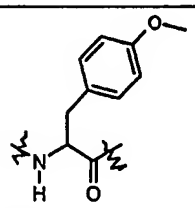
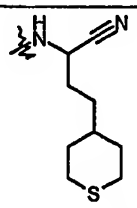
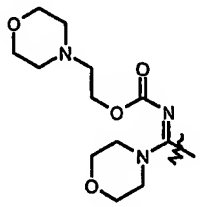
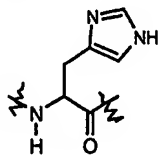
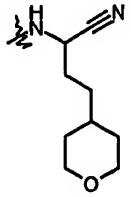
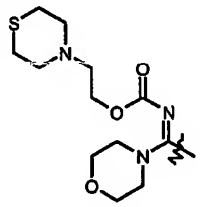
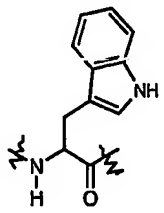
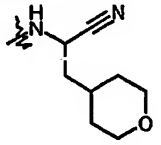
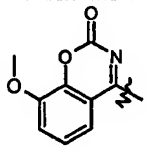
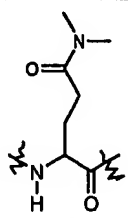
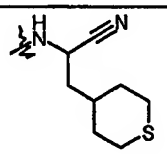
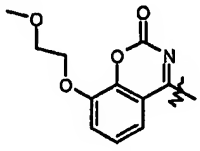
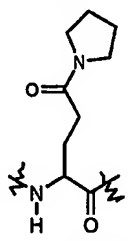
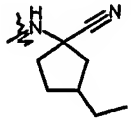
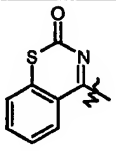
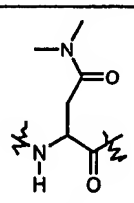
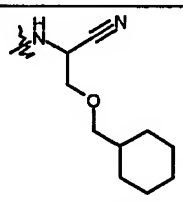
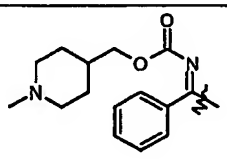
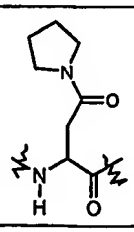
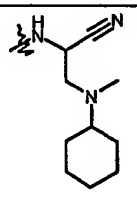
A6		B6		C6	
A7		B7		C7	
A8		B8		C8	
A9		B9		C9	
A10		B10		C10	
A11		B11		C11	
A12		B12		C12	

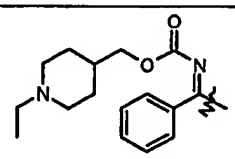
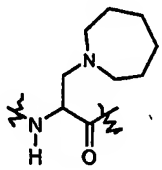
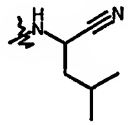
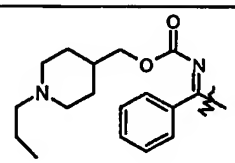
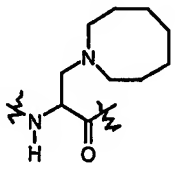
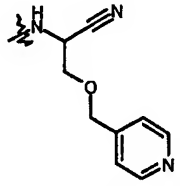
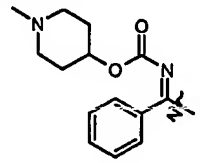
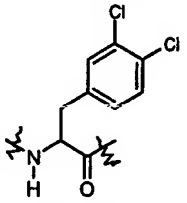
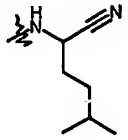
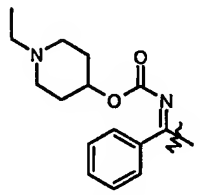
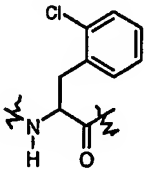
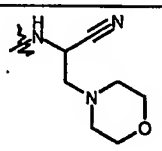
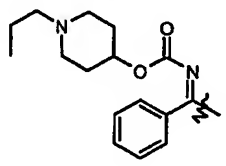
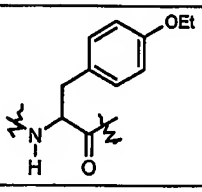
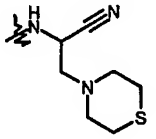
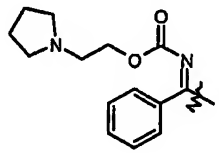
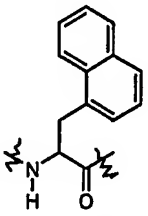
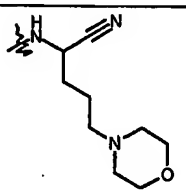
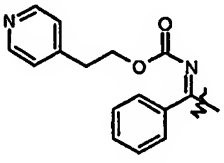
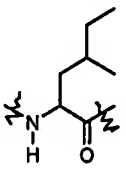
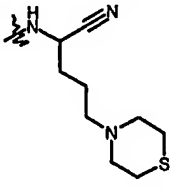
A14		B14		C14	
A15		B15		C15	
A16		B16		C16	
A17		B17		C17	
A18		B18		C18	
A19		B19		C19	
A20		B20		C20	

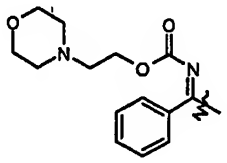
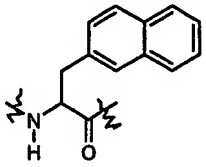
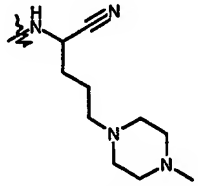
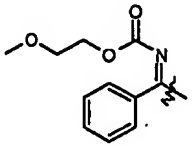
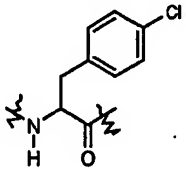
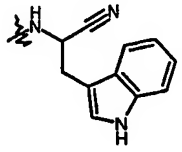
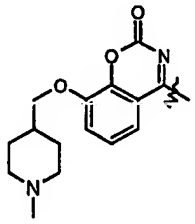
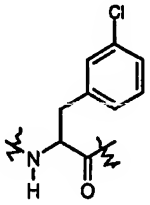
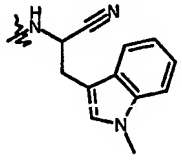
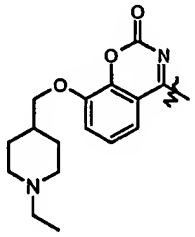
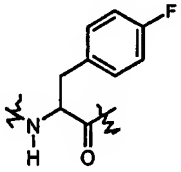
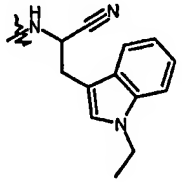
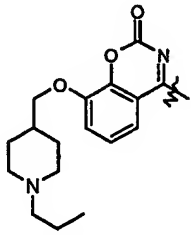
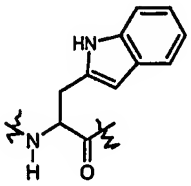
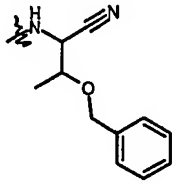
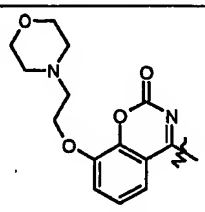
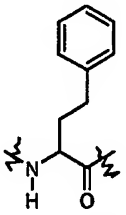
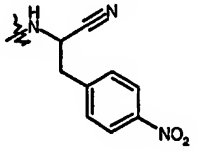
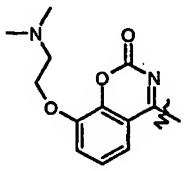
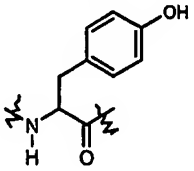
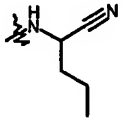
A21		B21		C21	
A22		B22		C22	
A23		B23		C23	
A24		B24		C24	
A25		B25		C25	
A26		B26		C26	
A27		B27		C27	

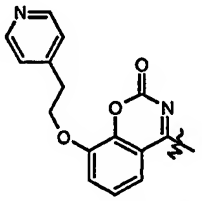
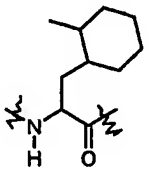
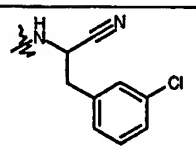
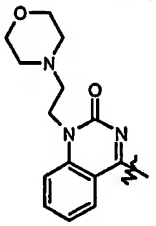
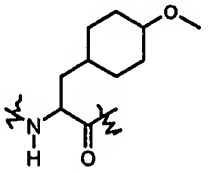
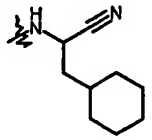
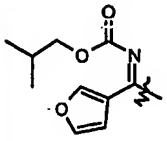
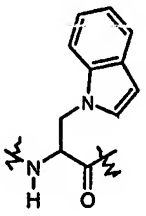
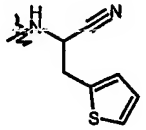
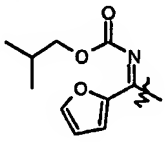
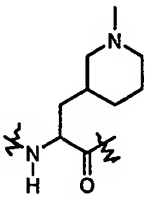
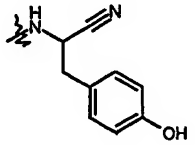
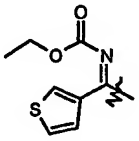
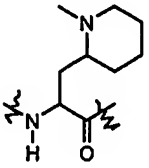
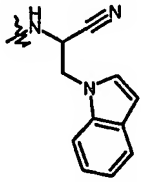
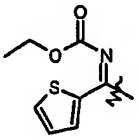
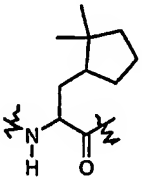
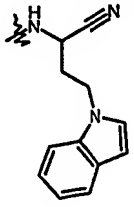
A28		B28		C28	
A29		B29		C29	
A30		B30		C30	
A31		B31		C31	
A32		B32		C32	
A33		B33		C33	
A34		B34		C34	

A35		B35		C35	
A36		B35		C36	
A37		B37		C37	
A38		B38		C38	
A39		B39		C39	
A40		B40		C40	
A41		B41		C41	

A42		B42		C42	
A43		B43		C43	
A44		B44		C44	
A45		B45		C45	
A46		B46		C46	
A47		B47		C47	
A48		B48		C48	

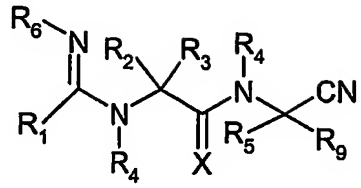
A49		B49		C49	
A50		B50		C50	
A51		B51		C51	
A52		B52		C52	
A53		B53		C53	
A54		B54		C54	
A55		B55		C55	

A56		B56		C56	
A57		B57		C57	
A58		B58		C58	
A59		B59		C59	
A60		B60		C60	
A61		B61		C61	
A62		B62		C62	

A63		B63		C63	
A64		B64		C64	
A65		B65		C65	
A66		B66		C66	
A67		B67		C67	
A68		B68		C68	

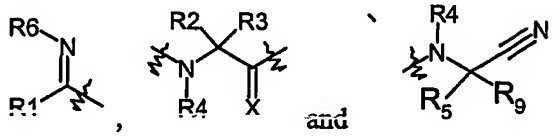
5

21. A compound of the formula (Ia)

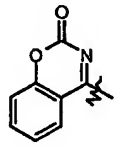
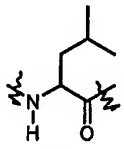
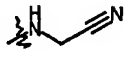
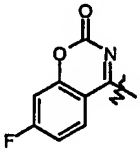
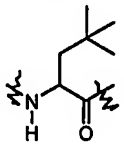
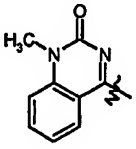
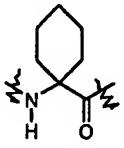
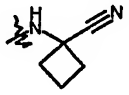
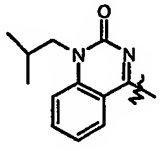
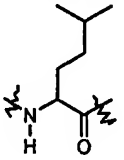
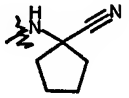


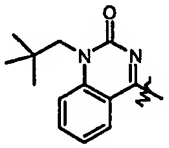
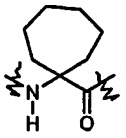
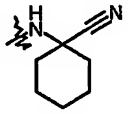
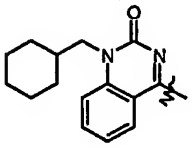
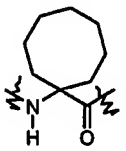
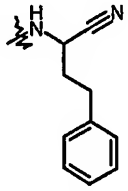
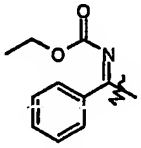
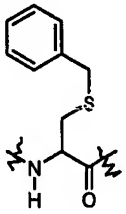
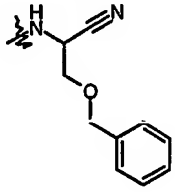
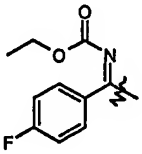
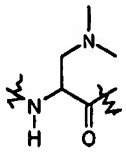
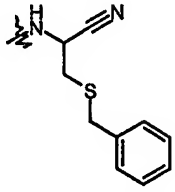
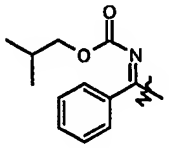
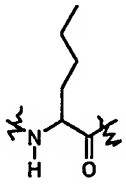
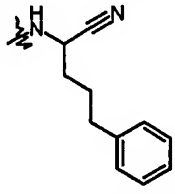
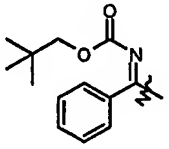
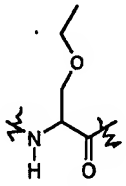
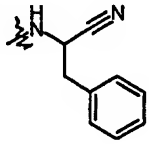
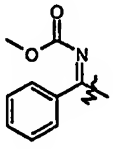
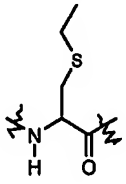
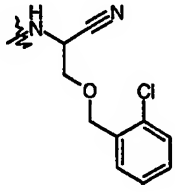
(Ia)

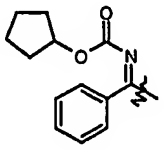
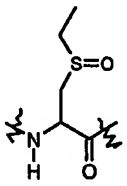
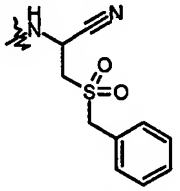
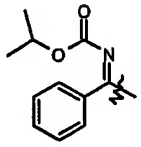
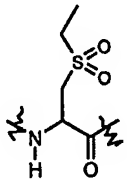
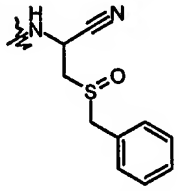
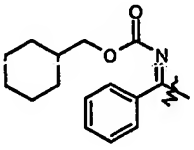
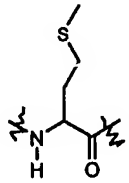
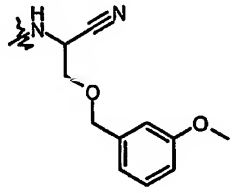
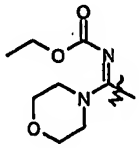
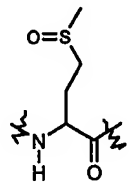
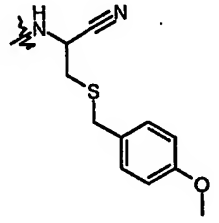
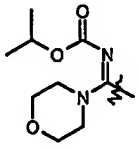
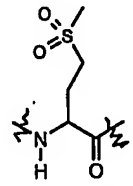
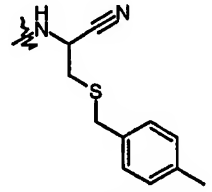
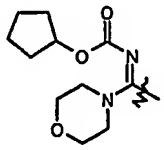
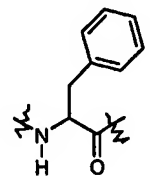
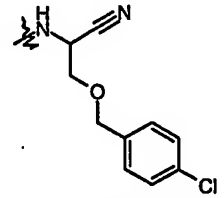
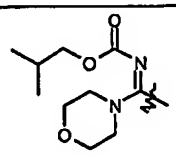
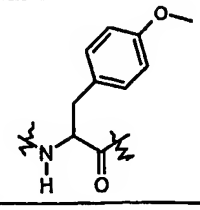
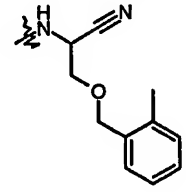
wherein for the formula (Ia), the components

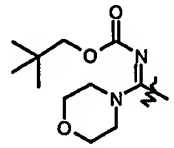
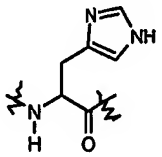
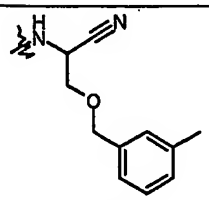
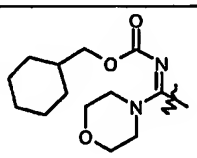
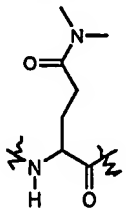
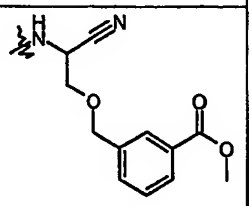
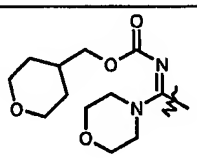
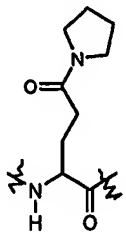
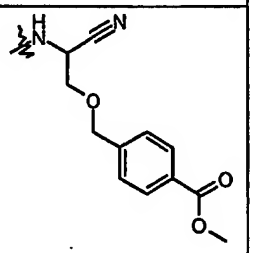
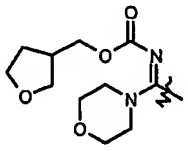
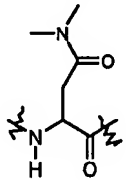
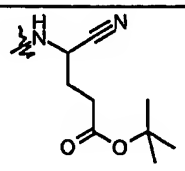
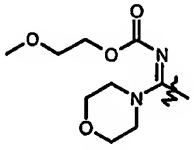
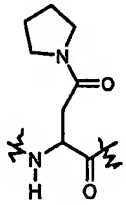
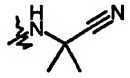
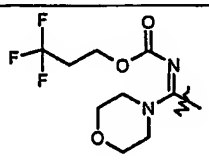
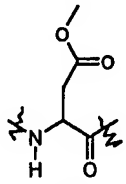
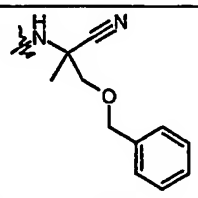
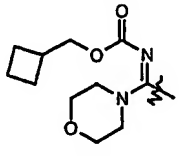
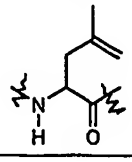
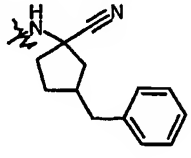


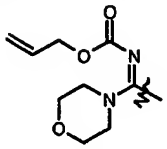
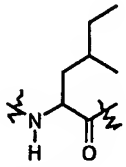
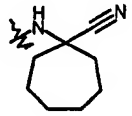
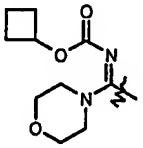
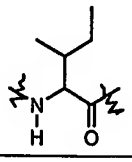
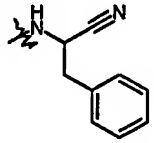
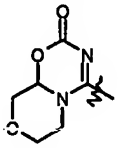
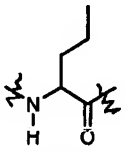
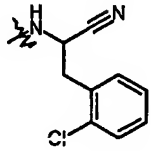
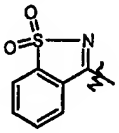
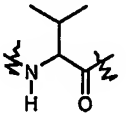
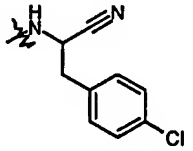
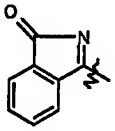
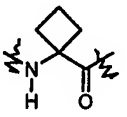
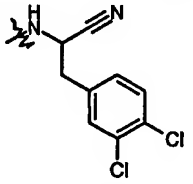
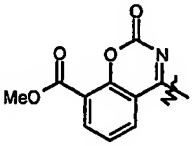
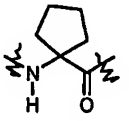
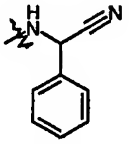
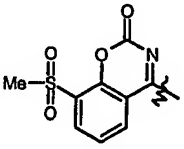
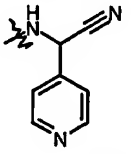
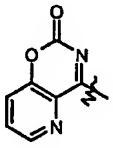
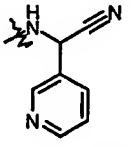
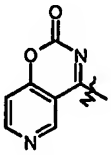
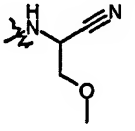
are chosen from any combination of A, B and C as follows:

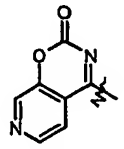
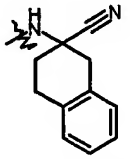
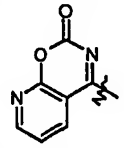
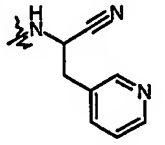
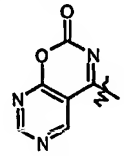
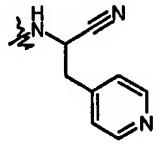
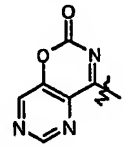
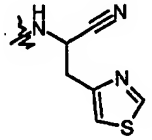
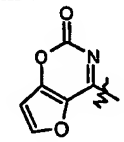
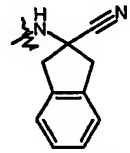
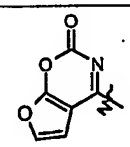
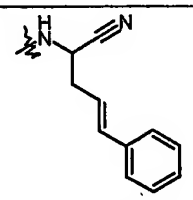
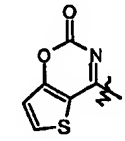
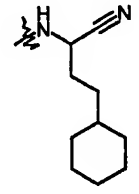
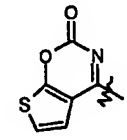
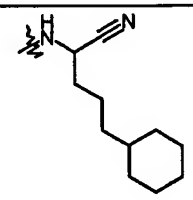
A		B		C	
A1		B1		C1	
A2		B2		C2	
A3		B3		C3	
A4		B4		C4	

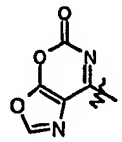
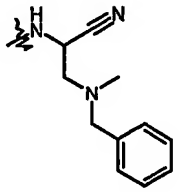
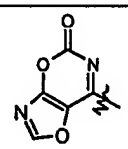
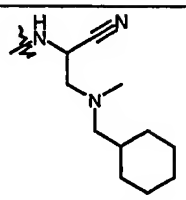
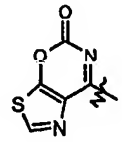
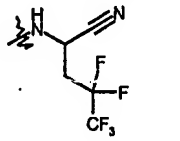
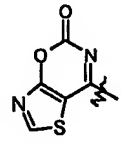
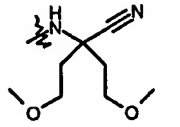
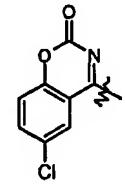
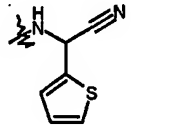
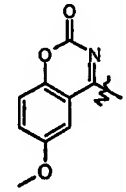
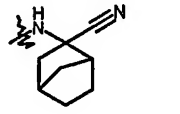
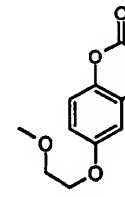
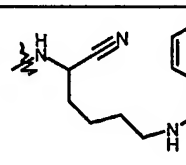
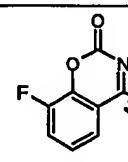
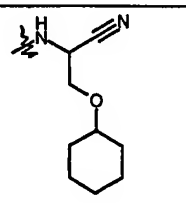
A5		B5		C5	
A6		B6		C6	
A7		B7		C7	
A8		B8		C8	
A9		B9		C9	
A10		B10		C10	
A11		B11		C11	

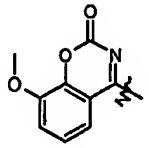
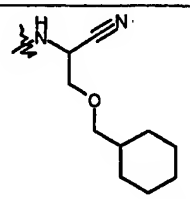
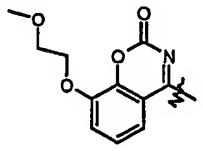
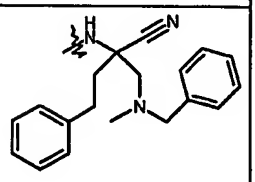
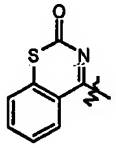
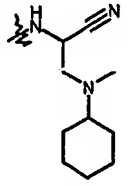
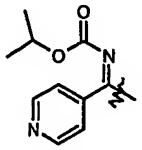
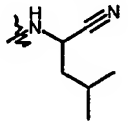
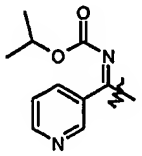
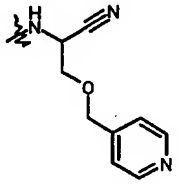
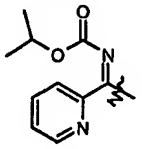
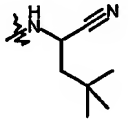
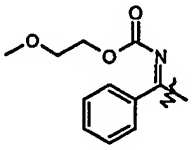
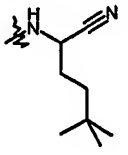
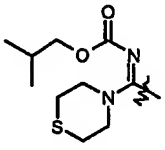
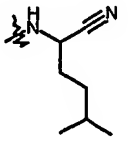
A12		B12		C12	
A13		B13		C13	
A14		B14		C14	
A15		B15		C15	
A16		B16		C16	
A17		B17		C17	
A18		B18		C18	

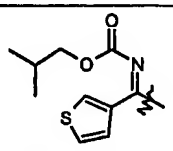
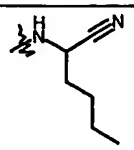
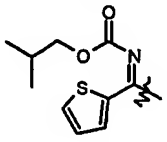
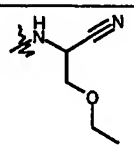
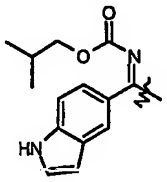
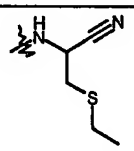
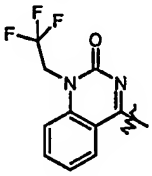
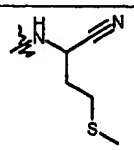
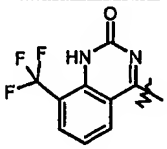
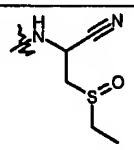
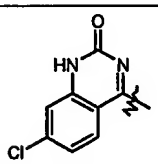
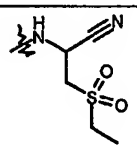
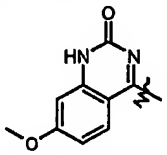
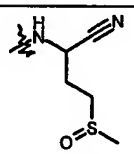
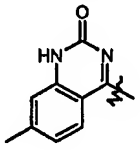
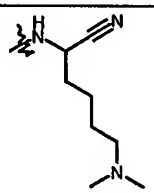
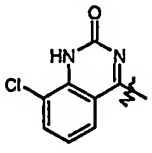
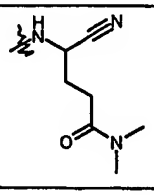
A19		B19		C19	
A20		B20		C20	
A21		B21		C21	
A22		B22		C22	
A23		B23		C23	
A24		B24		C24	
A25		B25		C25	

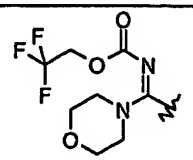
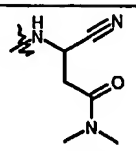
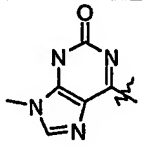
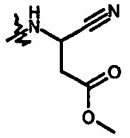
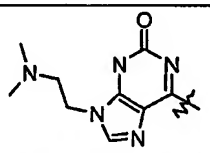
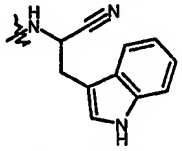
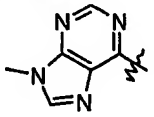
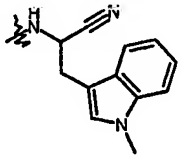
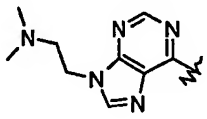
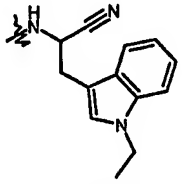
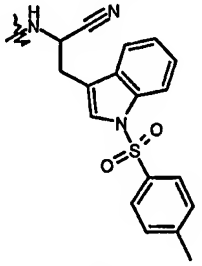
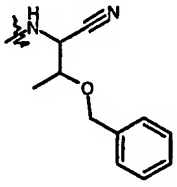
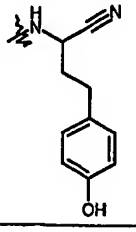
A26		B26		C26	
A27		B27		C27	
A28		B28		C28	
A29		B29		C29	
A30		B30		C30	
A31		B31		C31	
A32				C32	
A33				C33	
A34				C34	

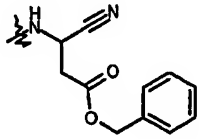
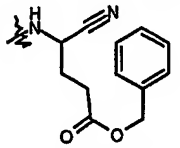
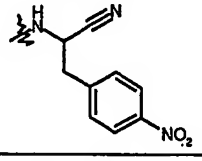
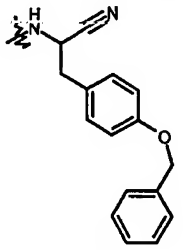
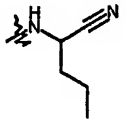
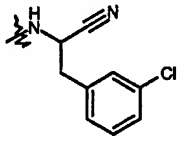
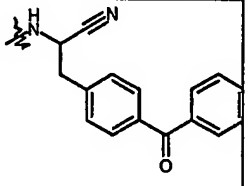
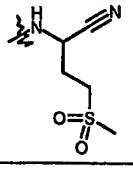
A35				C35	
A36				C36	
A37				C37	
A38				C38	
A39				C39	
A40				C40	
A41				C41	
A42				C42	

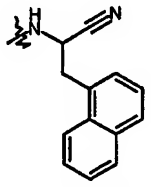
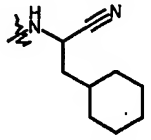
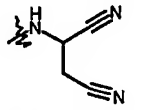
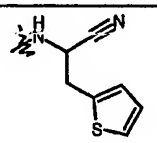
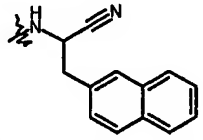
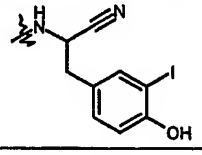
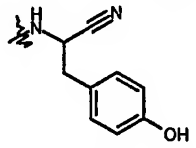
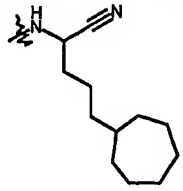
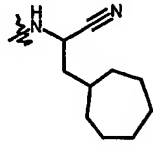
A43				C43	
A44				C44	
A45				C45	
A46				C46	
A47				C47	
A48				C48	
A49				C49	
A50				C50	

A51				C51	
A52				C52	
A53				C53	
A54				C54	
A55				C55	
A56				C56	
A57				C57	
A58				C58	

A59				C59	
A60				C60	
A61				C61	
A62				C62	
A63				C63	
A64				C64	
A65				C65	
A66				C66	
A67				C67	

A68				C68	
A69				C69	
A70				C70	
A71				C71	
A72				C72	
				C73	
				C74	
				C75	

				C76	
				C77	
				C78	
				C79	
				C80	
				C81	
				C82	
				C83	

				C84	
				C85	
				C86	
				C87	
				C88	
				C89	
				C90	
				C91	
				C92	
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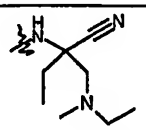
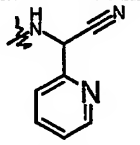
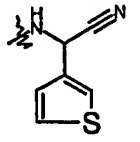
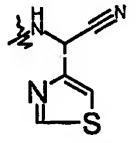
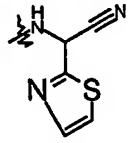
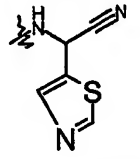
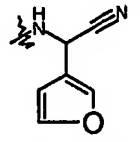
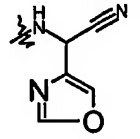
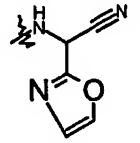
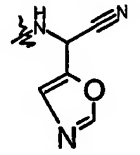
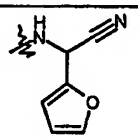
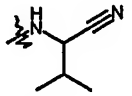
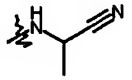
				C94	
				C95	
				C96	
				C97	
				C98	
				C99	
				C100	
				C101	
				C102	
				C103	

				C104	
				C105	
				C106	

or the pharmaceutically acceptable salts, esters, tautomers, individual isomers and mixtures of isomers thereof.

22. A compound chosen from:

({1-[(Benzyloxymethyl-cyano-methyl)-carbamoyl]-3,3-dimethyl-butylimino}-morpholin-4-yl-methyl)-carbamic acid ethyl ester;

{[1-(1-Cyano-3-phenyl-propylcarbamoyl)-3,3-dimethyl-butylimino]-morpholin-4-yl-methyl}-carbamic acid ethyl ester;

{[1-(Cyanomethyl-carbamoyl)-3,3-dimethyl-butylimino]-morpholin-4-yl-methyl}-carbamic acid cyclohexyl ester;

{[1-(1-Cyano-cyclopropylcarbamoyl)-3-cyclohexyl-propylimino]-morpholin-4-yl-methyl}-carbamic acid ethyl ester;

{[1-(Cyanomethyl-carbamoyl)-3,3-dimethyl-butylimino]-morpholin-4-yl-methyl}-carbamic acid tetrahydro-pyran-4-yl ester;

{[1-(1-Cyano-4-phenyl-butylcarbamoyl)-3,3-dimethyl-butylimino]-morpholin-4-yl-methyl}-carbamic acid ethyl ester;

{[1-(1-Cyano-cyclopropylcarbamoyl)-3,3-dimethyl-butylimino]-morpholin-4-yl-methyl}-carbamic acid 2-morpholin-4-yl-ethyl ester;

{[1-(1-Cyano-cyclopentylcarbamoyl)-4,4-dimethyl-pentylimino]-morpholin-4-yl-methyl}-carbamic acid ethyl ester;

{[1-(1-Cyano-cyclopentylcarbamoyl)-3,3,4-trimethyl-pentylimino]-morpholin-4-yl-methyl}-carbamic acid 2-methoxy-ethyl ester;

{[1-(1-Cyano-cyclopentylcarbamoyl)-3,3-dimethyl-butylimino]-morpholin-4-yl-methyl}-carbamic acid 2-isopropoxy-ethyl ester;

{[1-(1-Cyano-cyclopentylcarbamoyl)-3,3-dimethyl-butylimino]-morpholin-4-yl-methyl}-carbamic acid tetrahydro-furan-2-ylmethyl ester;

({1-[(Benzylsulfanylmethyl-cyano-methyl)-carbamoyl]-3,3-dimethyl-butylimino}-morpholin-4-yl-methyl)-carbamic acid isobutyl ester;

({1-[(Benzylsulfanylmethyl-cyano-methyl)-carbamoyl]-3,3-dimethyl-butylimino}-phenyl-methyl)-carbamic acid isobutyl ester;

({1-[(Benzyloxymethyl-cyano-methyl)-carbamoyl]-3,3-dimethyl-pentylimino}-phenyl-methyl)-carbamic acid isobutyl ester;

{[1-(1-Cyano-3-phenyl-propylcarbamoyl)-3,3-dimethyl-butylimino]-phenyl-methyl}-carbamic acid ethyl ester;

{[1-(Cyanomethyl-carbamoyl)-3,3-dimethyl-butylimino]-phenyl-methyl}-carbamic acid cyclohexyl ester;

{[1-(1-Cyano-cyclopropylcarbamoyl)-3-cyclohexyl-propylimino]-phenyl-methyl}-carbamic acid ethyl ester;

{[1-(Cyanomethyl-carbamoyl)-3,3-dimethyl-butylimino]-phenyl-methyl}-carbamic acid tetrahydro-pyran-4-yl ester;

{[1-(1-Cyano-4-phenyl-butylcarbamoyl)-3,3-dimethyl-butylimino]-phenyl-methyl}-carbamic acid ethyl ester;

{[1-(1-Cyano-cyclopropylcarbamoyl)-3,3-dimethyl-butylimino]-phenyl-methyl}-carbamic acid 2-morpholin-4-yl-ethyl ester;

{[1-(1-Cyano-cyclopentylcarbamoyl)-4,4-dimethyl-pentylimino]-phenyl-methyl}-carbamic acid ethyl ester;

{[1-(1-Cyano-cyclopentylcarbamoyl)-3,3,4-trimethyl-pentylimino]-phenyl-methyl}-carbamic acid 2-methoxy-ethyl ester;

{[1-(1-Cyano-cyclopentylcarbamoyl)-3,3-dimethyl-butylimino]-phenyl-methyl}-carbamic acid 2-isopropoxy-ethyl ester;

{[1-(1-Cyano-cyclopentylcarbamoyl)-3,3-dimethyl-butylimino]-phenyl-methyl}-carbamic acid tetrahydro-furan-2-ylmethyl ester;

{[1-(Cyanomethyl-carbamoyl)-2-(4-ethyl-4-methyl-cyclohexyl)-ethylimino]-morpholin-4-yl-methyl}-carbamic acid 1-methyl-piperidin-4-ylmethyl ester;

{[1-(1-Cyano-cyclopropylcarbamoyl)-2-(4-isopropyl-4-methyl-cyclohexyl)-ethylimino]-morpholin-4-yl-methyl}-carbamic acid 1-methyl-piperidin-4-ylmethyl ester;

{[1-(1-Cyano-cyclopentylcarbamoyl)-2-(4,4-diethyl-cyclohexyl)-ethylimino]-morpholin-4-yl-methyl}-carbamic acid 1-methyl-piperidin-4-ylmethyl ester;

{[1-(Cyanomethyl-carbamoyl)-4,4-dimethyl-pentylimino]-morpholin-4-yl-methyl}-carbamic acid 2-(1-methyl-piperidin-4-yl)-ethyl ester;

{[1-(1-Cyano-cyclopropylcarbamoyl)-4,4-dimethyl-hexylimino]-morpholin-4-yl-methyl}-carbamic acid 2-(1-methyl-piperidin-4-yl)-ethyl ester;

{[1-(1-Cyano-cyclopentylcarbamoyl)-3-cyclohexyl-propylimino]-morpholin-4-yl-methyl}-carbamic acid 2-(1-methyl-piperidin-4-yl)-ethyl ester;

{[1-(Cyanomethyl-carbamoyl)-3-(1-methyl-cyclopentyl)-propylimino]-morpholin-4-yl-methyl}-carbamic acid 2-(4-methyl-piperazin-1-yl)-ethyl ester;

{[1-(1-Cyano-cyclobutylcarbamoyl)-3-cyclopentyl-3-methyl-butylimino]-morpholin-4-yl-methyl}-carbamic acid 2-(4-methyl-piperazin-1-yl)-ethyl ester;

{[1-(1-Cyano-cyclopentylcarbamoyl)-3-cyclopentyl-propylimino]-morpholin-4-yl-methyl}-carbamic acid 2-(4-methyl-piperazin-1-yl)-ethyl ester;

4,4-Dimethyl-2-[1-(1-methyl-piperidin-4-yl)-2-oxo-2,3-dihydro-1*H*-quinazolin-4-ylideneamino]-pentanoic acid (1-cyano-cyclohexyl)-amide;

N-(1-Cyano-cyclohexyl)-3-cycloheptyl-2-[1-(1-methyl-piperidin-4-yl)-2-oxo-2,3-dihydro-1*H*-quinazolin-4-ylideneamino]-propionamide;

N-(1-Cyano-cyclohexyl)-3-cyclooctyl-2-{1-[2-(4-methyl-piperazin-1-yl)-ethyl]-2-oxo-2,3-dihydro-1*H*-quinazolin-4-ylideneamino}-propionamide;

2-[1-(2-Dimethylamino-ethyl)-2-oxo-2,3-dihydro-1*H*-quinazolin-4-ylideneamino]-4,4-dimethyl-pentanoic acid (1-cyano-cyclopentyl)-amide;

N-(1-Cyano-cyclopentyl)-2-[1-(3-dimethylamino-propyl)-2-oxo-2,3-dihydro-1*H*-quinazolin-4-ylideneamino]-3-(1,4,4-trimethyl-cyclohexyl)-propionamide;

N-Cyanomethyl-2-(4,4-dimethyl-cyclohexyl)-2-[2-oxo-1-(2-pyridin-4-yl-ethyl)-2,3-dihydro-1*H*-quinazolin-4-ylideneamino]-acetamide;

4-Methyl-4-(1-methyl-cyclopropyl)-2-[2-oxo-1-(3-pyrrolidin-1-yl-propyl)-2,3-dihydro-1*H*-quinazolin-4-ylideneamino]-pentanoic acid (1-cyano-cyclopentyl)-amide;

N-(1-Cyano-cyclopentyl)-4-(1-methyl-cyclopropyl)-2-[2-oxo-1-(3-piperidin-1-yl-propyl)-2,3-dihydro-1*H*-quinazolin-4-ylideneamino]-butyramide;

{[1-(1-Cyano-cyclohexylcarbamoyl)-2-cyclohexyl-ethylimino]-morpholin-4-yl-methyl}-carbamic acid 1-methyl-piperidin-4-ylmethyl ester;

{[1-(1-Cyano-cyclohexylcarbamoyl)-2-cyclohexyl-ethylimino]-morpholin-4-yl-methyl}-carbamic acid 2-(1-methyl-piperidin-4-yl)-ethyl ester;

{[1-(1-Cyano-cyclohexylcarbamoyl)-2-cyclohexyl-ethylimino]-morpholin-4-yl-methyl}-carbamic acid 2-(4-methyl-piperazin-1-yl)-ethyl ester;

{[1-(1-Cyano-cyclopentylcarbamoyl)-3,3-dimethyl-butylimino]-morpholin-4-yl-methyl}-carbamic acid 1-methyl-piperidin-4-ylmethyl ester;

[[1-(1-Cyano-cyclopentylcarbamoyl)-2-cycloheptyl-ethylimino]-(tetrahydro-pyran-4-yl)-methyl]-carbamic acid 2-dimethylamino-ethyl ester;

{[1-(Cyanomethyl-carbamoyl)-2-cyclooctyl-ethylimino]-morpholin-4-yl-methyl}-carbamic acid 3-dimethylamino-propyl ester;

{[1-(Cyanomethyl-carbamoyl)-3,3,4,4-tetramethyl-pentylimino]-morpholin-4-yl-methyl}-carbamic acid 2-pyridin-4-yl-ethyl ester;

{[1-(1-Cyano-cyclopentylcarbamoyl)-3,3,4-trimethyl-pentylimino]-morpholin-4-yl-methyl}-carbamic acid 3-pyrrolidin-1-yl-propyl ester;

{[1-(1-Cyano-cyclopentylcarbamoyl)-2-(1,4,4-trimethyl-cyclohexyl)-ethylimino]-morpholin-4-yl-methyl}-carbamic acid 3-piperidin-1-yl-propyl ester;

5,5-Dimethyl-2-[1-(1-methyl-piperidin-4-ylmethyl)-2-oxo-2,3-dihydro-1*H*-quinazolin-4-ylideneamino]-hexanoic acid cyanomethyl-amide;

4,4-Dimethyl-2-[1-(1-methyl-piperidin-4-ylmethyl)-2-oxo-2,3-dihydro-1*H*-quinazolin-4-ylideneamino]-pentanoic acid (1-cyano-cyclopropyl)-amide;

N-(1-Cyano-cyclopentyl)-3-cyclohexyl-2-[1-(1-methyl-piperidin-4-ylmethyl)-2-oxo-2,3-dihydro-1*H*-quinazolin-4-ylideneamino]-propionamide;

N-(Benzylsulfanylmethyl-cyano-methyl)-3-(4,4-diethyl-cyclohexyl)-2-{1-[2-(1-methyl-piperidin-4-yl)-ethyl]-2-oxo-2,3-dihydro-1*H*-quinazolin-4-ylideneamino}-propionamide;

4-Bicyclo[2.2.1]hept-1-yl-*N*-(1-cyano-3-phenyl-propyl)-2-{1-[2-(1-methyl-piperidin-4-yl)-ethyl]-2-oxo-2,3-dihydro-1*H*-quinazolin-4-ylideneamino}-butyramide;

4,4-Dimethyl-2-{1-[2-(1-methyl-piperidin-4-yl)-ethyl]-2-oxo-2,3-dihydro-1*H*-quinazolin-4-ylideneamino}-pentanoic acid (1-cyano-cyclopentyl)-amide;

N-(Benzyloxymethyl-cyano-methyl)-3-cyclohexyl-2-{1-[2-(4-methyl-piperazin-1-yl)-ethyl]-2-oxo-2,3-dihydro-1*H*-quinazolin-4-ylideneamino}-propionamide;

N-(1-Cyano-cyclopropyl)-3-cyclohexyl-2-{1-[2-(4-methyl-piperazin-1-yl)-ethyl]-2-oxo-2,3-dihydro-1*H*-quinazolin-4-ylideneamino}-propionamide;

4,4-Dimethyl-2-{1-[2-(4-methyl-piperazin-1-yl)-ethyl]-2-oxo-2,3-dihydro-1*H*-quinazolin-4-ylideneamino}-pentanoic acid (1-cyano-cyclopentyl)-amide;

(S)-5,5-Dimethyl-2-(2-oxo-2*H*-benzo[*e*][1,3]oxazin-4-ylamino)-heptanoic acid (1-cyano-cyclopropyl)-amide;

(S)-4,4-Dimethyl-2-(2-oxo-2*H*-benzo[*e*][1,3]oxazin-4-ylamino)-pentanoic acid (1-cyano-cyclopropyl)-amide;

(S)-4-methyl-2-(2-oxo-2*H*-benzo[*e*][1,3]oxazin-4-ylamino)-pentanoic acid (1-cyano-cyclopropyl)-amide;

(S)-2-(7-Fluoro-2-oxo-2*H*-benzo[*e*][1,3]oxazin-4-ylamino)-4,4-dimethyl-pentanoic acid (1-cyano-cyclopropyl)-amide;

(S)-5,5-Dimethyl-2-(1-methyl-2-oxo-1,2-dihydro-quinazolin-4-ylamino)-heptanoic acid (1-cyano-cyclopropyl)-amide;

(S)-4,4-Dimethyl-2-(1-methyl-2-oxo-1,2-dihydro-quinazolin-4-ylamino)-pentanoic acid (1-cyano-cyclopropyl)-amide;

(S)-4,4,5,5-Tetramethyl-2-(1-methyl-2-oxo-1,2-dihydro-quinazolin-4-ylamino)-hexanoic acid (1-cyano-cyclopropyl)-amide;

(S)-4,4,5,5-Tetramethyl-2-(2-oxo-2*H*-benzo[*e*][1,3]oxazin-4-ylamino)-hexanoic acid (1-cyano-cyclopropyl)-amide;

2-[(Acetylimino-phenyl-methyl)-amino]-N(benzyloxymethyl-cyano-methyl)-3-cyclohexyl-propionamide;

2-(7-Fluoro-2-oxo-*2H*-benxo[*e*][1,3]oxazin-4-ylamino)-5,5-dimethyl-heptanoic acid (1-cyano-cyclopropyl)-amide;

4-Methyl-2-(2-oxo-*2H*-benzo[*e*][1,3]oxazin-4-ylamino)-pentanoic acid (1-cyano-cyclopropyl)-amide;

2-(7-Fluoro-2-oxo-*2H*-benzo[*e*][1,3]oxazin-4-ylamino)-4-methyl-pentanoic acid (1-cyano-cyclopropyl)-amide;

N-(Cyano-dimethyl-methyl)-3-cyclohexyl-2-(2-oxo-*2H*-benzo[*e*][1,3]oxazin-4-ylamino)-propionamide;

N-(1-Cyano-cyclopropyl)-3-cyclohexyl-2-(2-oxo-*2H*-benzo[*e*][1,3]oxazin-4-ylamino)-propionamide;

N-(1-Cyano-cyclopropyl)-3-cyclohexyl-2-(7-fluoro-2-oxo-*2H*-benzo[*e*][1,3]oxazin-4-ylamino)-propionamide;

N-(Cyano-benzyloxymethyl -methyl)-3-cyclohexyl-2-(2-oxo-*2H*-benzo[*e*][1,3]oxazin-4-ylamino)-propionamide;

4,4-Dimethyl-2-(2-oxo-*2H*-benxo[*e*][1,3]oxazin-4-ylamino)-pentanoic acid (cyano-benzyloxymethyl-methyl)-amide;

2-(1,1-Dioxo-*1H*-1λ^6-benzo[*d*]isothiazol-3-ylamino)-4,4-dimethyl-pentanoic acid (cyano-benzyloxymethyl-methyl)-amide;

N-(Cyano-benzyloxymethyl-methyl)-3-cyclohexyl-2-(1,1-dioxo-*1H*-1λ^6-benzo[*d*]isothiazol-3-ylamino)-propionamide;

N-(1-Cyano-cylopropyl)-3-cyclohexyl-2-(1,1-dioxo-*1H*-1λ^6-benzo[*d*]isothiazol-3-ylamino)-propionamide;

N-(Cyano-dimethyl-methyl)-3-cyclohexyl-2-(1,1-dioxo-*1H*-1λ^6-benzo[*d*]isothiazol-3-ylamino)-propionamide;

2-(1,1-Dioxo-*1H*-1λ^6-benzo[*d*]isothiazol-3-ylamino)-4,4-dimethyl-pentanoic acid cyanomethyl-amide;

2-(1,1-Dioxo-*1H*-1λ^6-benzo[*d*]isothiazol-3-ylamino)-4,4-dimethyl-pentanoic acid (1-cyano-cyclopropyl)-amide;

2-(1,1-Dioxo-*1H*-1λ^6-benzo[*d*]isothiazol-3-ylamino)-4-methyl-pentanoic acid (1-cyano-cyclopropyl)-amide and

2-(1,1-Dioxo-*1H*-1λ^6-benzo[*d*]isothiazol-3-ylamino)-5,5-dimethyl-heptanoic acid (1-cyano-cyclopropyl)-amide

or the pharmaceutically acceptable salts, esters, tautomers, individual isomers and mixtures of isomers thereof.

23. A pharmaceutical composition comprising a pharmaceutically effective amount of a compound according to claim 1.

24. A method of modulating an autoimmune disease, said method comprising administering to a patient in need of such treatment a pharmaceutically effective amount of a compound according to claims 1 or 22.

25. The method according to claim 24 wherein the autoimmune disease is rheumatoid arthritis, systemic lupus erythematosus, Crohn's disease, ulcerative colitis, multiple sclerosis, Guillain-Barre syndrome, psoriasis, Grave's disease, myasthenia gravis, scleroderma, glomerulonephritis, dermatitis, endometriosis or insulin-dependent diabetes mellitus.

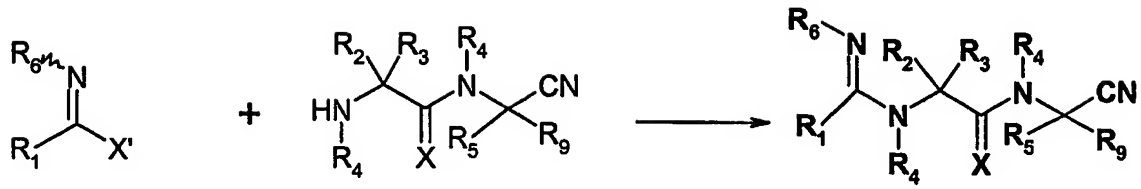
26. A method of treating Alzheimer's disease comprising administering to a patient in need of such treatment a pharmaceutically effective amount of a compound according to claim 1.

27. A method of treating atherosclerosis comprising administering to a patient in need of such treatment a pharmaceutically effective amount of a compound according to claim 1.

28. A method of treating osteoporosis comprising administering to a patient in need of such treatment a pharmaceutically effective amount of a compound according to claim 14.

29.A method of treating asthma comprising administering to a patient in need of such treatment a pharmaceutically effective amount of a compound according to claim 1.

30. A process of making a compound of the formula (Ia) according to the equation:



(X) (III) (Ia)

wherein for the formula (Ia), R_1, R_2, R_3, R_4, R_5, R_6, R_9 and X are as defined in claim 1, said process comprising:

reacting a dipeptide nitrile intermediate of the formula (III) shown above, or a basic salt thereof, with a compound intermediate of the formula X shown above, wherein X' is an appropriate leaving group, with or without an appropriate base to provide the product compound of the formula(Ia).